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A Concurrent Comparison of Home and Sanatorium Treatment of Pulmonary Tuberculosis in South India

TUBERCULOSIS CHEMOTHERAPY CENTRE, MADRAS

In India, as in most under-developed countries, the tuberculosis problem is aggravated by an acute shortage of sanatorium beds. The number of active cases of tuberculosis in the country has been estimated at 2 ½ million, but only 23 000 tuberculosis beds are available. In these circumstances great importance attaches to the possibility of applying mass domiciliary chemotherapy as a substitute for sanatorium treatment in cases of pulmonary tuberculosis. The findings of the present study, based on a comparison of the two types of treatment over a period of 12 months, show that despite the manifest advantages of sanatorium care—rest, adequate diet, nursing and supervised medicine-taking—the merits of domiciliary chemotherapy are comparable to those of sanatorium treatment, and that it would therefore be appropriate to treat the majority of patients at home, provided an adequate service were established.

I. INTRODUCTION

GENERAL

A controlled comparison of the merits of home treatment with those of sanatorium treatment for pulmonary tuberculosis for a period of 12 months has been completed at the Tuberculosis Chemotherapy Centre, Madras, and the following is a report of the results up to the end of this period. A follow-up of the patients is being undertaken, and the findings will be reported at a later date.

The Centre was set up in 1956 under the joint auspices of the Indian Council of Medical Research (ICMR), the Madras State Government, the World Health Organization (WHO) and the Medical Research Council of Great Britain (MRC). The senior scientific staff of the Centre, who are responsible for the work reported here, are: Dr Wallace Fox (WHO), Senior Medical Officer; Drs R. H. Andrews (WHO), C. V. Ramakrishnan (ICMR), and S. Velu (Madras Government), Medical Officers; Dr S. Devadatta (ICMR), Assistant Medical Officer; Drs A. L. Bhatia (ICMR), D. A. Mitchison (WHO) and J. B. Selkon (WHO), Bacteriologists; Dr P. R. J. Gangadharam (ICMR), Assistant Bacteriologist; Miss E. Holst (WHO), Laboratory Technician; Mr. T. V. Subbaiah (ICMR), Laboratory Research Assistant; Mr. S. Radhakrishna (Madras Government), Statistician.

The research of the Centre is guided by a Project Committee consisting of three ICMR representatives (Drs P. V. Benjamin, Convenor, J. Frimodt-Møller and K. S. Sanjivi), the Director of the ICMR (Dr C. G. Pandit), the Director of Medical Services, Madras State (first Lt Col. Sangham Lal and then Dr V. R. Thayumanaswamy), a WHO representative (appointed for each meeting), an MRC representative (appointed for each meeting) and the Senior Medical Officer of the Centre (Dr Wallace Fox). The joint secretaries are Mrs K. Daniels and Mr B. S. Verma.

The MRC, through its Tuberculosis Research Unit, is responsible for the scientific direction of the research, in accordance with plans prepared by the Project Committee. Dr Wallace Fox of the Tuberculosis Research Unit has been seconded to WHO to serve as the Senior Medical Officer and the Director of Research at the Centre, and the laboratory was established by Dr D. A. Mitchison of the MRC Group for Research on Drug Sensitivity in Tuberculosis. Close contact is maintained between the Centre in Madras, the MRC Tuberculosis

Research Unit (Dr P. D'Arcy Hart) and the Group for Research on Drug Sensitivity in Tuberculosis (Drs D. A. Mitchison, J. B. Selkon and J. G. Wallace) in London. Dr Ian Sutherland of the MRC Statistical Research Unit has advised on statistical aspects. In India, Drs Ida B. Scudder and J. Frimodt-Møller acted as independent radiological assessors, and Drs C. Gopalan and V. N. Patwardhan of the ICMR Nutritional Research Unit have advised on the dietary study referred to in this report.

The present investigation was made in the Tuberculosis Chemotherapy Centre, Madras, and in the Madras Government Tuberculosis Sanatorium, Tambaram. Although the sanatorium patients in the investigation were Chemotherapy Centre patients, and under the direction of the Centre's medical staff, the sanatorium staff was responsible for the administration and day-to-day clinical supervision of this group of patients. The sanatorium staff concerned were: Medical Superintendents—Dr C. S. Sadasivam, then Dr M. A. Hamid and then Dr P. R. Mudaliar; Resident Medical Officers—Dr A. R. Krishnamurthy, then Dr A. K. Nambiar, and then Dr B. Narayanakudubi; Medical Officers—Drs A. S. Aswathaman, K. Chandrasekaran, T. K. Deivanayagam, L. A. Murthy, S. S. Nathan and Smt. Indira Sambasivam; Honorary Physicians—Drs D. Damodar Dass and K. Vasudeva Rao. The majority of the patients admitted to the study were referred to the Centre from the Government Tuberculosis Institute, Madras, the Director during the period of intake being Dr P. R. Mudaliar. The analysis was undertaken and the report was prepared in the Tuberculosis Chemotherapy Centre by the Centre's medical and statistical staff, Dr Wallace Fox and Mr. S. Radhakrishna being the co-ordinators.

FORMATION OF THE CENTRE

In October 1955, at the request of the Government of India, WHO sponsored the visit to India of three representatives of the MRC to advise on studies designed to provide information on the mass domiciliary application of chemotherapy in the treatment of pulmonary tuberculosis. This was a problem of great importance, since India, which has only 23 000 tuberculosis beds, has been estimated to have at least 2½ million active cases of tuberculosis (Benjamin, 1946), and a national sample survey conducted by the ICMR indicates that there are 1½ million infectious cases in the country (Indian Council of Medical Research, 1959). The Indian authorities were, however, disturbed by the possibility that chemotherapy at home might prove inadequate in the treatment of the disease and that a high proportion of patients so treated might become chronic excretors of drug-resistant organisms. This might represent a serious public health risk if chemotherapy in the home were widespread. The MRC representatives (Drs J. G. Scadding, P. D'Arcy Hart and Wallace Fox) held many discussions with the Indian and the WHO authorities and attended a meeting of the Tuberculosis Sub-Committee of the ICMR where the practicability of controlled studies was discussed. In the course of the discussions it was agreed that it would be premature, with the knowledge then available, to begin with the mass domiciliary application of chemotherapy, even in a limited area. It was decided, initially, to undertake controlled comparative studies of the treatment of patients and to supervise their contacts. The patients were to be recruited through routine diagnosis by the chest clinic service of a large city. Following negotiations with the Madras State authorities it was decided to locate the Centre in Madras City.

At the invitation of the ICMR and WHO, the MRC undertook scientific responsibility for the studies. WHO provided eight international staff members—namely, a Senior Medical Officer, a Medical Officer, a Bacteriologist, a Laboratory Technician, two Public Health Nurses, an X-ray Technician and an Administrative Officer. WHO also provided equipment and supplies, including a static X-ray apparatus with a tomographic attachment, a 70-mm photofluorographic apparatus and dark-room equipment, all the major equipment for a laboratory for the diagnosis of tuberculosis and identification of acid-fast organisms, the equipment for an animal-house and the apparatus necessary for virulence tests, much of the equipment for the out-patient clinic, office and statistical equipment, scientific books and journals, and means of transport, which included one jeep, and two ambulances and five small station wagons for the domiciliary service. All the radiographic supplies and antituberculosis drugs were also supplied by WHO.

More than 40 of the staff members were Madras Government employees and more than 60 were employed by the ICMR. This large staff included national counterparts to some of the WHO staff, as well as health visitors, statisticians, social workers, a nutritionist, laboratory and clerical workers, radiography and ancillary staff. The Madras Gov-

ernment provided newly constructed premises for the Centre, undertook a number of structural alterations, some independently and some jointly with the ICMR, and was responsible for the upkeep of the premises. An animal-house was constructed jointly by the Madras Government and the ICMR. Many supplies and expendables, including feed for the experimental animals and all drugs, apart from antituberculosis drugs, and much equipment obtainable in India, were provided jointly by the Madras Government and the ICMR, and so were petrol and servicing for the vehicles. A fund was established by the ICMR to provide financial assistance to individual families when this was considered to be essential. Finally, 100 sanatorium beds were made available for the study by the Madras Government, which also undertook the expense of their upkeep. The responsibilities for this complex arrangement were defined in a Plan of Operations made under an agreement between the WHO and the Government of India.

The Centre began to treat patients in May 1956, in a series of pilot investigations. The first study to be based on a random allocation of treatment started in September 1956, and is described in the present report.

GENERAL OBJECTS OF THE STUDY

The study was designed to yield information on the following aspects of the treatment of pulmonary tuberculosis among patients living in an adverse urban environment in India:

(1) The relative merits of home and sanatorium treatment with standard chemotherapy.

(2) The extent to which the infectivity of a series of patients treated at home can be reduced by standard chemotherapy.

(3) The prevalence of tuberculosis in family contacts at the time of diagnosis of the index case and the subsequent incidence of tuberculosis among them, with particular reference to the drug sensitivity of the strains.

(4) The identity and virulence of the causative organisms and their comparison with strains of tubercle bacilli from England.

(5) Some of the practical procedures involved in the mass application of chemotherapy—for example, methods of sputum collection, of checking the self-administration of medicines and of general supervision of patients.

(6) Diet and its relation to the response to chemotherapy.

(7) The causes and management of treatment failures.

The present report is concerned principally with the first two of these points. The others will be considered fully in later reports.

II. GENERAL PLAN AND CONDUCT OF THE STUDY

SOURCE OF CASES

It was considered fundamental that the patients admitted to treatment in the Centre should be selected from those attending at local chest clinics because of symptoms, since the great majority of tuberculous patients diagnosed in India present in this way. Mass miniature radiography was not used as a routine source of cases, although it happened that a small number of the study patients (all with symptoms) had originally been diagnosed by mass miniature radiography. The majority of patients came from the Government Tuberculosis Institute, which is the main tuberculosis clinic in Madras City and is immediately adjacent to the Centre. It was arranged that whenever a patient, on a first visit to the Government Tuberculosis Institute, presented any radiographic abnormality and gave an address which was in a defined geographical area of intake, he was referred to the Centre for further investigation. Patients considered suitable for the study in the Centre, according to the criteria set out below, were admitted to treatment; the rest were referred back to the Government Tuberculosis Institute.

There are five other tuberculosis clinics in Madras City, and attempts were also made to refer patients who lived in the area of intake from these clinics to the Centre for further investigation. Although this proved rather difficult to organize, some patients from these other clinics were admitted to the present study. A further source of cases was the Employees' State Insurance (ESI) scheme, a compulsory contributory health insurance scheme. Arrangements were made for all suspected cases of pulmonary tuberculosis in ESI members in the

Madras City area to be investigated by the Centre. The arrangements were, however, completed late in the period of intake and only a few ESI members were admitted to the present study.

Most of the patients came from the poorest sections of the population of Madras City.

AREA OF INTAKE

Madras City, with a total area of 50 square miles [1] and a population of approximately 1 750 000, had, at the time of this study, 50 administrative divisions, which were distributed among the six tuberculosis clinics. The area from which patients were admitted was initially restricted to the nine divisions (14 square miles) allocated to the Government Tuberculosis Institute. The area of intake gradually increased until it incorporated the whole of 15 divisions and parts of eight more. The limits of the final area of intake were approximately three miles west of the Centre, three miles north, two miles east and five miles south and its extent was approximately 20 square miles, the population approaching 750 000.

DEFINITION OF ELIGIBLE CASES

With certain exceptions listed below, a patient with pulmonary tuberculosis was eligible for the study if he or she satisfied all the following conditions:

(1) The patient had either had no previous antituberculosis chemotherapy, or antituberculosis chemotherapy had been administered for not more than two weeks.

(2) The patient was aged 12 years or more (sanatorium beds were not available for younger children).

(3) The sputum was positive for tubercle bacilli either on direct smear examination or on culture.

(4) The patient was living in Madras City in the defined area of intake (and was thus accessible for home visiting) and was likely to remain so for several years.

(5) The patient was prepared to:

(*a*) accept treatment either at home or in sanatorium for at least a year

(*b*) accept treatment whether with pills or injections

(*c*) permit home visiting.

(6) The family was judged to be co-operative.

[1] 1 square mile = 2.6 km²

By adopting these criteria it was hoped to admit both newly diagnosed cases and old cases which had had no previous chemotherapy (or very little), to be able to treat them for at least 12 months, and to follow them up for a further four years. In addition it was the intention to examine all the close contacts of each patient, by both radiography and tuberculin testing, at regular intervals over the five-year period. Findings on these contacts will be published separately.

A patient was considered ineligible for the study if any of the following applied at the start of treatment:

(1) The patient was too ill for home treatment (e.g., was nearly moribund, had a spontaneous pneumothorax or had had a severe haemoptysis).

(2) The patient had a pleural effusion obscuring more than one-third of a lung field, as seen on a postero-anterior chest radiograph.

(3) The patient had a non-respiratory form of tuberculosis which it was considered would complicate treatment.

(4) The patient was known to have leprosy.

(5) The patient was known to have a serious concomitant disease, such as diabetes.

(6) The patient was known to be pregnant.

A random selection of radiographs, taken on admission of the patients to treatment in the present study, is reproduced in the Appendix.

THE TREATMENT COMPARISON

In the present study a comparison was made between the results of treatment at home and in sanatorium for a period of 12 months. Two series of patients were treated with isoniazid and the sodium salt of para-aminosalicylic acid (sodium PAS), given together, one series being treated at home and the other in sanatorium. The form, prescribed dosage and rhythm of the drug combination were the same for both series. It will be appreciated that sanatorium treatment represented rest, good nursing, good accommodation, supervised administration of medicine and a good diet; in contrast, home treatment, in the patients under study, meant less rest, little or no nursing, in the main inferior accommodation, unsupervised and less regular administration of medicine and an inferior diet. It is shown in sections XI and XII of this report that these disadvantages to the series treated

at home were substantial. The study therefore represented a comparison of a standard drug combination, used on the one hand under optimal conditions in sanatorium, and on the other hand under conditions of everyday life in a large Indian city. All the treatment for every patient, whether at home or in sanatorium, was free.

PRETREATMENT INVESTIGATIONS

The following investigations were made before the start of treatment in the present study:

(1) Clinical examination and assessment of the general clinical condition.

(2) A full-plate postero-anterior chest radiograph.

(3) Weight (pounds).

(4) Erythrocyte sedimentation rate (ESR Westergren 200 mm, reading in mm at 1 hour).

(5) An intracutaneous tuberculin (Mantoux) test with 5 tuberculin units (TU) of a purified protein derivative (PPD) on the left arm. If there was less than 10 mm induration in the greatest diameter at 48 or 72 hours, a 100 TU test was undertaken on the right arm and this was also read at 48 or 72 hours.

(6) Examination of the urine for albumin and sugar.

(7) Measurement or estimate of the 24-hour volume of sputum.

(8) Recording of the character of the sputum as purulent, muco-purulent or mucoid.

(9) The examination by direct smear and culture of a minimum of four sputum specimens, two produced on demand and within a matter of minutes in the Centre and two produced overnight in the home. The degree of positivity both on smear and culture was graded.

(10) Drug-sensitivity tests to isoniazid, PAS and streptomycin on two cultures, one from a specimen produced in the Centre, the other from an overnight specimen.

In addition to the above, a detailed inquiry was made into previous chemotherapy.

Before accepting a patient for treatment it was very important to establish that both the patient and the family would co-operate in the allocated treatment, whether this proved to be at home or in sanatorium. The co-operation to be expected was assessed both in the Centre and in the home by the health visitors, public health nurses, social workers and doctors. At least one visit to the home was paid by a health visitor and one by a doctor, and, if necessary, also by a social worker, during the period of assessment. Following this essential preparatory assessment, all the patients allocated to sanatorium treatment accepted admission to sanatorium and all those allocated to treatment at home were so treated. There were, however, some discharges from treatment during the course of the 12 months, and these are reported in section XIII.

ALLOCATION OF TREATMENT

The allocation of treatment was made from a prearranged list, prepared by the MRC Statistical Research Unit, which was based on random sampling numbers and which had been incorporated in a series of numbered sealed envelopes before the start of the study. The allocation was made by the Centre's statistical staff from the next sealed envelope in the series. Neither the medical nor statistical staff nor anybody else in the Centre had prior knowledge of the treatment which any individual patient would receive.

The first allocation was made on 24 September 1956, and the intake stopped on 24 September 1957, by which date 193 patients had been allocated to treatment, 96 at home and 97 in sanatorium.

THE STANDARD CHEMOTHERAPY

The standard medicament was dispensed in the form of cachets, each containing 25 mg of isoniazid and 1.25 g of the sodium salt of PAS. The dosage, which depended on the weight of the patient, was as follows:

Weight of patient		*Number of cachets*		*Total daily dosage*	
(lb.)	*(kg)*	*morning*	*evening*	*isoniazid (mg)*	*PAS (sodium salt) (g)*
100 or more	(45.4 or more)	4	4	200	10.00
80-99	(36.3-45.3)	3	4	175	8.75
< 80	(< 36.3)	3	3	150	7.50

If a patient gained weight and moved into a higher category the dosage was increased at the next monthly examination. However, if a patient lost weight and moved into a lower category, the dosage was not lowered.

Table 1 sets out in detail the dosage of drugs in relation to body-weight. It will be seen that with few exceptions (only six of the 193 patients weighed more than 110 lb. (50 kg) before treatment) the initial dosage of isoniazid was greater than 4 mg/kg

TABLE 1
DAILY DOSAGE OF DRUGS IN RELATION TO BODY-WEIGHT

Body-weight (lb.) (kg)	Actual amount of drug given daily		Daily dosage in relation to body-weight		Number of patients (before treatment)
	isoniazid (mg)	PAS (sodium salt) (g)	isoniazid (mg/kg body-weight)	PAS (sodium salt) (g/kg body-weight)	
50–59 (22.7–27.1)	150	7.50	6.6–5.6	0.33–0.28	11
60–69 (27.2–31.7)			5.5–4.8	0.27–0.24	22
70–79 (31.8–36.2)			4.7–4.2	0.23–0.21	42
80–89 (36.3–40.7)	175	8.75	4.8–4.4	0.24–0.22	63
90–99 (40.8–45.3)			4.3–3.9	0.21–0.19	36
100–109 (45.4–49.8)	200	10.00	4.4–4.1	0.22–0.20	13
110–119 (49.9–54.3)			4.0–3.7	0.19	6

body-weight. For 11 patients who weighed less than 60 lb. (27 kg) before treatment the initial dosage of isoniazid exceeded 5.5 mg/kg. The mean dosage of isoniazid at the start of treatment was 4.6 mg/kg. The dosage of PAS ranged from about 0.2 g/kg to 0.3 g/kg body-weight, with a mean value of 0.23 g/kg at the start of treatment. Thus the dosage of both drugs was considerably higher in terms of the body-weight of these South Indian patients than the dosage represented by the combination isoniazid 200 mg daily plus PAS (sodium salt) 10 g daily in European patients, whose average weight is greater. (This dosage was used in the MRC isoniazid trial (Great Britain, Medical Research Council, 1953b, 1955).)

HOME TREATMENT

In this study home treatment meant the treatment of patients in their own homes, with clinic supervision of their progress. Chemotherapy was started immediately after allocation of the treatment and the majority of the home patients attended the Centre weekly throughout the 12 months for supplies of medicine. In addition a visit was usually paid to the home each week during the first month by a health visitor, and less regularly by a doctor or a public health nurse. Less frequent home visits were made in later months. It was rare for fewer than two home visits to be made each month, because one was made to deliver a sputum specimen bottle and one — an unexpected visit — to collect a specimen of urine to be tested for the presence of PAS, as a check that the patient was taking the medicine.

Patients initially too ill to attend weekly rested at home for the first month and were then brought up by ambulance for re-examination and assessment. As soon as they had improved sufficiently they were changed to the ordinary routine of visits to the Centre and the home.

SANATORIUM TREATMENT

Patients allocated to treatment in sanatorium were admitted with a minimum of delay, and almost always within a week of the allocation of treatment. Chemotherapy was started immediately after admission. The sanatorium was the Government Tuberculosis Sanatorium, Tambaram, which is the main sanatorium for Madras State and is 16 miles away from Madras City. The patients came under the day-to-day supervision of the sanatorium staff. Regular visits were made to the sanatorium by the medical staff of the Centre, and every patient was seen weekly. In addition, regular visits were paid by the Centre's health visitors and a social worker.

REST

Home patients were encouraged (if working) to stop work initially and to rest, and the majority did so, although rest was rarely strict except in patients feeling really ill. The majority of the patients were ambulant much of the time and were quite often not at home when visited, especially if

the visit was a surprise one. When patients were considered medically fit to return to work, they were encouraged to do so. However, a number of patients returned to work before the Centre's staff considered them medically fit.

In contrast, the sanatorium patients rested in bed in the early months, being allowed up only for toilet. After three or four months they were usually allowed up two hours a day, and by six months some were up four hours a day. After completing six months' chemotherapy the sanatorium patients were allowed, if sufficiently fit, to go home once a month, from six in the morning until six in the evening, and the majority availed themselves of this privilege.

ASSESSMENTS OF PROGRESS

At monthly intervals after the start of chemotherapy, all the patients in both series had assessments which included (1) a postero-anterior radiograph, (2) an estimate of sputum volume, (3) a description of the sputum character, (4) two or more examinations of sputum by smear and culture, (5) in addition (from three months onwards) a pair of laryngeal swabs for culture, (6) sensitivity tests to isoniazid and PAS on one positive culture, (7) the ESR, (8) the weight, and (9) an assessment of the degree of ambulation and working capacity. At six and 12 months after the start of chemotherapy every sanatorium patient was brought to the Centre and re-examined by its staff to ensure that the assessments at these important dates were obtained by the same techniques and with the same equipment as were used in the home series.

URINE TESTING FOR PAS

In order to check the self-administration of drugs in the home series a ferric chloride test for PAS (Simpson, 1956) was performed on urine specimens obtained at every clinic visit and later, in addition, at planned visits to the home, and, later still, at surprise visits to the home. In the sanatorium series a urine specimen was tested weekly for each patient. (Since acetylsalicylic acid and salicylates may also produce positive results to this test they were not prescribed for patients in the study.)

POWDERED MILK

During the course of the study a free supply of powdered milk was made available, through a relief organization, for patients under treatment in the tuberculosis clinics in the city and for their families. Therefore, although it had been intended to make as little change as possible in the diet of the study families, it became necessary to give powdered milk to these families; this supplement was given to the families whether the patient was under treatment at home or in sanatorium.

Beginning in the middle of March 1957, 1 lb.[1] was given monthly to each patient living alone at home, 2 lb. to a family of two, and 4½ lb. to a family of three or more. The quantity of milk powder was reduced in June 1957 to the following monthly quantities, which were maintained throughout the rest of the study:

One person	½ lb.
Family of 2	1 lb.
Family of 3 to 5	2 lb.
Family of 6 to 8	3 lb.
Family of 9 or more	4½ lb.

In giving milk powder it was stressed that it was intended for consumption by the contacts rather than by the patients, and in this way it was hoped to ensure the distribution of the milk powder among the whole family. A dietary study, reported briefly in section XII (page 106) below, showed that this supplement of powdered milk did not appreciably diminish the differences in diet between the home and sanatorium series.

III. BACTERIOLOGICAL PROCEDURES

GENERAL

The frequency of the bacteriological investigations varied during the 12-month period and was modified on several occasions early in the course of the study. The final procedure adopted, which applied to most of the monthly examinations and to the majority of the patients, was as follows. Before the start of treatment a minimum of four sputum specimens was obtained. These four specimens comprised two overnight (" collection ") specimens and two clinic (" spot ") specimens—that is, specimens which were produced on demand in the Centre. At the end of the first and second months of treatment two collec-

[1] 1 lb. = 0.45 kg

tion specimens of sputum were obtained from each patient. At the end of three months and monthly thereafter two collection specimens, and, in addition, a pair of laryngeal swabs, were obtained. In the early stages of the study a monthly spot specimen was also obtained from each patient, but this procedure was later stopped (except for the pretreatment specimens). All the sputum specimens were examined by smear and by culture. The laryngeal swabs were examined by culture only.

A number of factors were responsible for the evolution of this somewhat complex pattern of bacteriological investigation. Before the start of treatment it was essential to assess the patients rapidly and to make a bacteriological diagnosis with a minimum number of clinic visits. Hence spot specimens, which were produced immediately in the Centre, were obtained in addition to the overnight collection specimens. The spot specimens were also a precaution against misleading pretreatment sensitivity test results, which might have arisen if patients had " borrowed " sputum from chronic cases in order to obtain admission to treatment. For this reason one of the two tests for sensitivity to isoniazid, PAS and streptomycin, which were undertaken on all patients before treatment, was always performed on a culture of a spot specimen, the other being performed on a collection specimen. Both spot and collection specimens were obtained for each patient at the monthly examinations during treatment, until the superiority of collection specimens (Andrews & Radhakrishna, 1959) had been established. The spot specimens during treatment were then discontinued, especially as there was less reason for a patient to " borrow " sputum once treatment had started. Laryngeal swab cultures were introduced when facilities became available and when it became evident that some patients experienced difficulty in producing sputum as treatment progressed. It was decided to obtain multiple specimens to ensure that at least one uncontaminated culture result was obtained for each patient each month (contamination of cultures by moulds and fungi is notoriously common in India). Moreover, the greater the number of cultures set up the greater was the chance of obtaining a positive culture for drug-sensitivity tests. The number of cultures was reduced to two at one and two months, when the proportion of positive results obtained at these months was found to be high. Finally, with multiple cultures each month, it was possible to diagnose bacteriological quiescence at the end of 12 months of treatment on a much firmer basis than if single cultures only had been obtained monthly.

In addition to following an identical pattern of investigation for home and sanatorium patients, every effort was made to ensure identical procedures for the collection and examination of the bacteriological specimens from both series of patients. Thus, the sanatorium sputum specimens were delivered daily early in the morning to the Centre's laboratory and were processed alongside the specimens from the home patients which were received during the same morning, the laboratory staff being unaware whether any individual specimen had been obtained from a home or a sanatorium patient. On only a very few occasions was there any delay in delivery of the sputum specimens from the sanatorium to the Centre. In order to avoid differences in the method of collection of laryngeal swab specimens for the two series, the members of the Centre's medical staff who took the laryngeal swab specimens from all the home patients also visited the sanatorium in turn to take the specimens from the sanatorium series. The specimens were then stored in an ice-box and delivered within two hours to the Centre's laboratory for processing.

BACTERIAL CONTENT OF SPUTUM

Sputum smears were made on new glass slides, which were used once only, and were examined by fluorescence microscopy. The ability of this method to detect tubercle bacilli has been shown to be fully as good as conventional Ziehl-Neelsen microscopy in the Centre's laboratory (Holst, Mitchison & Radhakrishna, 1959). Positive smears were graded as 3-plus, 2-plus and 1-plus according to the average number of bacilli seen per field. A 3-plus smear contained more than 5000 bacilli per mm^2—that is, about 100 bacilli per field examined with a total magnification of $\times 700$. A 1-plus smear was recorded when there were fewer than about 300 bacilli per mm^2—that is, six bacilli per field under the same magnification; a 2-plus smear, therefore, contained between 5000 and 300 bacilli per mm^2.[1]

[1] These estimates were obtained by selecting samples of smears considered to be borderline between the 3-plus and 2-plus grades and 2-plus and 1-plus grades respectively. These smears were then restained by the Ziehl-Neelsen method and counts were obtained of the average number of bacilli per randomly selected field. Fluorescence microscopy was not used for these counts since bacilli rapidly lose their fluorescence, and thus disappear from view, during the lengthy exposure to light necessary for counting a heavily positive field.

The procedure for culture was as follows. The sputum specimens were treated with 4% sodium hydroxide and centrifuged. The total period of contact with the alkali was 35 minutes. The centrifuged deposit was then washed with distilled water (which had been shown in the Centre's laboratory not to be bactericidal for tubercle bacilli for a period of at least two hours), with the aim of diluting the concentrate and thus preventing a carry-over of an effective quantity of antituberculosis drugs to the culture medium. The deposit was inoculated with a loop on to two slopes of Löwenstein-Jensen medium. The slopes were examined weekly for eight to nine weeks and were reported as negative if no growth was present by that time. Growth typical of *Mycobacterium tuberculosis* was recorded as 3-plus if it was confluent, 2-plus if there were innumerable discrete colonies, and 1-plus if there were 100-20 colonies; and the number of colonies was recorded if this was less than 20.

The procedure for culture of laryngeal swabs was as follows. The two laryngeal swabs taken from each patient were treated together, being decontaminated in 4% sulphuric acid for 10 minutes and then neutralized by immersion in 1% sodium hydroxide for one minute. Each swab was then rubbed on to the surface of a single slope of Löwenstein-Jensen medium. The slopes were examined and reported on in the same way as the sputum cultures.

A sample of these cultures has been examined by a variety of methods to confirm their identity and the results will be reported elsewhere. A further check was obtained as to the identity of the organisms, both before treatment and at subsequent months, from the pattern of sensitivity results and also from the catalase activity of growth which occurred on drug-free or on isoniazid-containing slopes. Not only are atypical mycobacteria resistant to one or more of the chemotherapeutic drugs, isoniazid, PAS and streptomycin (Tarshis et al., 1955; Wolinsky et al., 1957; Selkon & Mitchison, 1959), but the catalase activity of their growth on medium with and without isoniazid is usually higher than for tubercle bacilli (Coster & Manten, 1956; Bönicke, 1958). If any doubt as to the identity of the organisms arose as a result of the sensitivity tests or catalase activity, the cultures were investigated further.

The results of the bacteriological examinations at the end of any month of treatment were accepted only if they were performed on specimens collected not more than seven days before or after the appropriate date. Apart from the laryngeal swab results only complete tests were accepted—that is, tests for which the results of both the smear and the culture examination for tubercle bacilli were available.

SENSITIVITY TESTS

Sensitivity tests to isoniazid, PAS and streptomycin were performed on two cultures before the start of treatment, one from a spot and one from a collection specimen. After the start of treatment, sensitivity tests to isoniazid and PAS (but not, as a routine, to streptomycin) were performed on one culture at every month for which positive cultures were obtained.

Procedures

The techniques employed were similar to those described for isoniazid by the MRC (Great Britain, Medical Research Council, 1953a), for PAS by Mitchison & Monk (1955) and for streptomycin by Stewart (1955). Sensitivity tests were set up from the diagnostic cultures within two or three days of their becoming positive. If growth was insufficient, the cultures were reincubated to allow enough organisms to grow for preparation of the inoculum. The inoculum suspension was made by adding approximately 2 mg (moist weight) of bacilli, obtained as a representative sample from all parts of the growth, to ¼-oz screw-capped bottles containing 0.5 ml of sterile distilled water and glass beads, and then shaking the bottle mechanically for one minute. Standard 3-mm loopfuls of this suspension were inoculated on to Löwenstein-Jensen medium slopes containing the concentrations of the drugs set out below, as well as on to a drug-free slope as a control. The standard sensitive strain, H37Rv, was also set up with each series of tests and, if more than one batch of medium was used during the course of the series of tests, it was set up for each batch. The drug concentrations employed for strain H37Rv covered a serial range of twofold dilutions above and below the minimal inhibitory concentration expected for this strain, as well as a drug-free slope as a control.

	Drug concentrations in µg/m
Isoniazid:	
Test strain	0.2 1, 5, 50
H37Rv	0.025, 0.05, 0.1, 0.2, 1
Sodium PAS dihydrate:	
Test strain	2, 4, 8, 16, 64
H37Rv	0.25, 0.5, 1, 2, 4
Streptomycin:	
Test strain	4, 8, 16, 32, 1024
H37Rv	1, 2, 4, 8

The term " growth " has been used to mean the presence of 20 or more colonies on any slope. If the control (drug-free) slope yielded 100 or fewer colonies, the result was ignored and the test was repeated. Strain H37Rv was usually inhibited by 0.1 or 0.2 μg/ml isoniazid, by 1 or 2 μg/ml sodium PAS dihydrate, and by 4 μg/ml streptomycin. The results of PAS- and streptomycin-sensitivity tests were expressed as resistance ratios—namely, the minimal drug concentration inhibiting growth of the test strain divided by the minimal drug concentration inhibiting strain H37Rv. If growth was obtained on the slope containing 0.2 μg/ml isoniazid but not on that containing 1 μg/ml, or if the resistance ratio to PAS or streptomycin was 4, the test was repeated.

Definitions of bacterial drug resistance

Isoniazid (1) *Pretreatment tests.* Resistance was defined as growth on 1 μg/ml or a higher concentration, or growth on 0.2 μg/ml, provided that a repeat test on the same strain yielded growth on 0.2 μg/ml or a higher concentration. One exception only was made for a patient in whom pretreatment sensitivity tests to isoniazid on two cultures, obtained from sputum specimens on different days, both yielded growth on 0.2 but not on 1 μg/ml, although a repeat test of each showed inhibition by 0.2 μg/ml. This patient was classified as having resistant organisms, since the probability of obtaining growth on 0.2 μg/ml from two separate specimens in the Centre's laboratory, if both strains were really sensitive, was of the order of 1 in 20 000.

(2) *Post-treatment tests.* The definition of resistance was the same as for the pretreatment tests. However, 11 strains obtained after the start of treatment yielded growth on 0.2 μg/ml, and the result of a repeat test was not available. In these circumstances, the strain has been called resistant. This interpretation was adopted because in a series of 35 repeat tests on strains growing on 0.2 but not on 1 μg/ml, 29 strains yielded growth on 0.2 μg/ml or a higher concentration, and only six were inhibited by 0.2 μg/ml in the repeat test.

PAS (1) *Pretreatment tests.* In the great majority of patients, sensitivity test results were available on two separate cultures. The patient's cultures have been regarded as being resistant before treatment if any test yielded a resistance ratio of more than 8, or if there were two tests, one of which yielded a resistance ratio of 8 and the other 4 or more, or if three resistance ratios of 4 were obtained from among the tests on the two pretreatment cultures and the two repeat tests on those cultures.

(2) *Post-treatment tests.* Since only one post-treatment strain was tested monthly from each patient, the post-treatment definition of resistance was different from that before treatment. A strain was called resistant if the result of a test was either a resistance ratio of 8 or more, or a resistance ratio of 4, followed by a ratio of 4 or more in a repeat test. In six instances, where a result of a repeat test was not available for a strain with a resistance ratio of 4, the strain has been classified as sensitive. This interpretation was adopted because in a series of 53 repeat tests on strains with a resistance ratio of 4, 43 yielded resistance ratios of 2 or less.

Streptomycin pretreatment tests. A strain was considered resistant if a resistance ratio of 8 or more was obtained, or a resistance ratio of 4, followed by a ratio of 4 or more in a repeat test.

IV. THE PATIENTS ALLOCATED TO TREATMENT

CLASSIFICATION

Although 193 patients were allocated to treatment, it was later discovered that a number were, for various reasons which will now be described, not suitable for inclusion in the main comparison between home and sanatorium treatment.

(1) For some patients it was discovered after the start of treatment that, although they had been considered at the time of allocation to conform to the definitions of suitability, they did not in fact do so; for example, some patients were found to have had previous chemotherapy of more than two weeks' duration.

(2) Other patients, although conforming to the initial criteria, were for other reasons later found not to be suitable for the main comparison; for example, some had isoniazid-resistant organisms or PAS-resistant organisms before treatment.

(3) It was intended to give uninterrupted chemotherapy, either at home or in the sanatorium, in accordance with the random allocation, for 12

months. This did not always prove possible; for example, some patients were discharged prematurely from sanatorium.

The main analysis in the present report is therefore concerned with the comparison of those patients in the two treatment series who conformed to the following especially important criteria: (*a*) of having, before treatment, organisms sensitive to the drugs used; (*b*) of having had, as far as is known, no previous chemotherapy (in a few instances, up to two weeks' chemotherapy); and (*c*) of having followed the prescribed regime for 12 months with, at most, minor variations.

The patients who are not included in this main analysis, whatever the reason, are also of importance; such patients would certainly be encountered in any mass campaign against tuberculosis. Many of them were examined monthly, and all were examined clinically, radiographically and bacteriologically at 12 months. Information on them will therefore be presented in several subsidiary analyses (in section XIII).

The classification of the patients into the main and subsidiary groups is presented in Table 2. The main analysis concerns 82 of the 96 patients allocated to treatment at home and 81 of the 97 allocated to treatment in sanatorium. Thus, 14 home and 16 sanatorium patients have not been included in the main analysis but contribute to seven subsidiary groups as shown in the table. Some patients had more than one feature which required their separation from the main analysis, and such patients appear in more than one of the subsidiary groups. This explains why the figures in Table 2 for the subsidiary groups of home patients add up to a total of 18, although only 14 patients were involved.

PRETREATMENT COMPARISON BETWEEN THE HOME AND SANATORIUM SERIES

The procedure for the random allocation of treatment (section II, page 55) was rigorously observed, but it was later found that the two series had by chance differed before the start of treatment in important radiographic and bacteriological respects.

Age, sex and religion

The age and sex distributions of the patients are given in Table 3. The left-hand section refers to the

TABLE 2
NUMBERS OF PATIENTS IN THE MAIN AND SUBSIDIARY ANALYSES

	Home	Sanatorium	Both series	Sections of the report in which these groups of patients are considered
Total patients allocated to treatment	96	97	193	IV, X, XII
Patients in the main analysis : namely, those with organisms sensitive to isoniazid and PAS, who had had no chemotherapy or at most two weeks of previous chemotherapy and who were treated for 12 months as allocated.*	82	81	163	IV—IX, XI, XII
Patients in the subsidiary analyses : namely, those with				
(*a*) Isoniazid-resistant organisms before treatment**	6	3	9	
(*b*) PAS-resistant organisms before treatment**	4	2	6	
(*c*) Previous chemotherapy of more than two weeks' duration, but with organisms sensitive to isoniazid and PAS	2	2	4	XIII
(*d*) Non-tuberculous deaths from diseases which influenced the course of the tuberculosis	1	1	2	
(*e*) Failure of desensitization, or prolonged desensitization, to PAS	1	1	2	
(*f*) Premature discharge from treatment	1	7	8	
(*g*) Hospital or sanatorium stay of more than six weeks (home patients only)	3	—	3	

* Four patients (two home, two sanatorium) with streptomycin-resistant strains before treatmen are included in the main, analysis, since the standard chemotherapy did not include streptomycin.
** In the present study

TABLE 3
DISTRIBUTION OF THE PATIENTS ACCORDING TO AGE, SEX AND RELIGION

Age in years (estimated)	Patients included in the main analysis						All patients allocated to treatment					
	home			sanatorium			home			sanatorium		
	male	female	total	male	female	total	male	female	total	male	female	total
12-14	1	0	1	0	0	0	1	0	1	1	0	1
15-24	12	10	22	18	15	33	17	11	28	22	16	38
25-34	16	15	31	10	9	19	18	15	33	14	9	23
35-44	7	6	13	9	6	15	11	7	18	12	6	18
45-54	10	1	11	9	1	10	11	1	12	10	2	12
55 or more	3	1	4	4	0	4	3	1	4	5	0	5
All ages	49	33	82	50	31	81	61	35	96	64	33	97
Religion												
Hindu	38	30	68	38	21	59	49	31	80	51	23	74
Moslem	6	1	7	5	4	9	7	1	8	6	4	10
Christian	5	2	7	7	6	13	5	3	8	7	6	13

patients included in the main analysis and the right-hand section to all the patients allocated to treatment. Considering the main analysis first, it will be seen that 49 males and 33 females were allocated to treatment at home, the corresponding figures in sanatorium being 50 and 31. The distributions of estimated ages are reasonably similar, although there were rather fewer patients, both male and female, in the 15-24 age-group in the home series (12 males and 10 females) than in the sanatorium series (18 males and 15 females), while the position was reversed in the 25-34 age-group (16 male and 15 female home patients, and 10 male and 9 female sanatorium patients). The same pattern is shown by the figures for all the patients allocated to treatment.

With regard to the religion of the patients (Table 3), the numbers of Hindus, Moslems and Christians among the males were very similar in the two series. Among the female patients in the main analysis, on the other hand, there were more Hindus in the home series—namely, 30, compared with 21 in sanatorium; there were one Moslem and two Christians in the home series, compared with four Moslems and six Christians in sanatorium. The same pattern occurs for all the patients allocated to treatment.

Clinical, radiographic and bacteriological condition

Table 4 shows the condition of the patients at the time of admission to treatment, as reflected by their general condition, the weight (pounds) and the ESR—all of which were assessed in the Centre before the allocation of treatment—the bacterial content of the sputum on smear and on culture, and

TABLE 4

CONDITION ON ADMISSION TO TREATMENT

	Patients included in the main analysis				All patients allocated to treatment			
	males		females		males		females	
	home	san.	home	san.	home	san.	home	san.
Number of patients	49	50	33	31	61	64	35	33
General condition :								
Good	8	3	3	5	10	3	3	5
Fair	31	34	19	17	39	45	20	19
Poor	8	13	10	6	9	16	11	6
Very poor	0	0	0	1	0	0	0	1
No information	2	0	1	2	3	0	1	2
Weight (lb.) : *								
Under 60	3	1	2	3	3	2	3	3
60-69	0	1	11	8	1	1	11	9
70-79	7	9	12	9	9	10	13	10
80-89	22	15	6	10	26	21	6	10
90-99	12	15	2	1	16	17	2	1
100-109	3	7	0	0	4	9	0	0
110 or more	2	2	0	0	2	4	0	0
ESR (mm in 1 hr) :								
0-10	1	1	0	1	1	1	0	1
11-20	0	0	0	2	0	1	0	2
21-50	9	8	3	4	12	8	3	4
51-100	31	28	21	15	39	36	23	16
101 or more	8	13	9	9	9	18	9	10
Extent of cavitation:								
Nil	6	5	3	2	6	6	3	2
Slight	7	13	2	4	7	16	2	4
Moderate	17	16	9	18	23	20	10	18
Extensive	19	16	19	7	25	22	20	9
Number of lung zones involved in disease:								
1	1	0	1	0	1	0	1	0
2	6	10	1	2	6	11	1	2
3	4	8	4	6	6	11	4	7
4	11	13	9	11	13	19	9	11
5	13	10	9	4	18	11	9	4
6	14	9	9	8	17	12	11	9
Bacterial content of sputum: **								
Direct smear negative, culture negative	1	0	1	1	1	0	1	1
Direct smear negative, culture less than 20 colonies	3	3	0	2	3	3	0	2
Direct smear negative, culture 20 colonies or more	0	5	1	2	1	8	2	2
Direct smear positive,								
1-plus (scanty)	4	9	4	5	4	11	4	7
2-plus (moderate)	12	11	12	13	16	17	13	13
3-plus (heavy)	29	22	15	8	36	25	15	8

* 1 lb. = 0.45 kg

** These are the results of single collection specimens, except for nine male patients (five home and four sanatorium), all in the main analysis, for whom special estimates of bacterial content were made from results of spot specimens (see page 64).

the extent of cavitation and the number of lung zones involved in disease. A sample, selected at random, of 10 pretreatment radiographs is reproduced in the Appendix.

The extent of cavitation and the number of lung zones involved in disease were reported from a full-plate radiograph by an independent assessor (Dr Ida B. Scudder), who was unaware of the treatment series of any patient. The assessor graded the extent of cavitation on each film as extensive, moderate, slight or nil, and then checked the consistency of the grading by reviewing the films, in batches, grade by grade (Fox & Sutherland, 1956). She assessed the number of lung zones involved in disease, using standard definitions of zones (Daniels et al., 1948), and recording the presence of *any* disease in each zone, no matter how limited in extent.

The bacterial content of the sputum was graded on the result for a single collection specimen of sputum, except for nine patients for whom the result for a collection specimen was not available. For these nine patients (five males at home and four males in sanatorium) the results for spot specimens (produced in the Centre) were available. It was important to have a uniform pretreatment assessment of bacterial content of the sputum for *all* the patients, to use in analyses later in this report. The results for the spot specimens for these nine patients were therefore used to estimate the expected bacterial content of a collection specimen of the sputum. These estimates were based on the relationship between the positivity of pretreatment spot and collection specimens in the 154 patients in the main analysis, for whom both types of specimen were available. The net result was that two 1-plus positive smear results for the spot specimens were estimated as 2-plus results for collection specimens, and five 2-plus and two 3-plus results for the spot specimens were estimated as 3-plus results for collection specimens.

All these assessments are presented both for the patients in the main analysis and for all the patients allocated to treatment ; the comparisons between the treatment series are similar for these two groups of patients, and are thus described below only for the patients in the main analysis.

The distributions for the males and females in the main analysis in respect of general condition, weight and ESR were reasonably similar. (It should be noted that the average weight of the male patients was only 87.4 lb. (39.6 kg) and of the females only 73.4 lb. (33.3 kg).) The position in respect of extent of cavitation, the number of lung zones involved in disease, and the bacterial content of the sputum, was less satisfactory. Considering the males first, there was little to choose between the two groups in respect of moderate and extensive cavitation, although the involvement of lung zones and the results of sputum examinations suggested that the home males had, as a group, rather worse disease, but the differences are not notable. Turning to the females, however, it appeared that the home series was at a substantial disadvantage, particularly in extensive cavitation, in which respect the difference between the two series attained statistical significance.

In view of these findings, it was considered essential to confirm the radiographic differences. For this purpose it was decided to introduce other types of assessment. A second assessor (Dr J. Frimodt-Møller), who was also unaware of the treatment series of any patient, assessed the full-plate radiographs, using a scoring procedure, to determine both cavitation and the total extent of disease. The basis of the scores used was as follows. Each lung was considered to have only two lobes, the middle lobe being regarded as part of the upper lobe. A maximum score of 45 points was possible for the total extent of disease in each lobe, of which a maximum of 20 was for cavitation ; the scores for cavitation were recorded separately from those for the total extent of the disease.

The assessments of cavitation and the total extent of the disease by the scoring procedure are set out in Table 5. For convenience in comparison, the original assessments of cavitation by the grading procedure and the number of lung zones involved in disease (made by Dr Ida B. Scudder) are also given in Table 5. Considering cavitation first, the scoring findings are consistent with those of the grading procedure, both for the males and for the females. Thus, 28 males at home and 27 in sanatorium had scores of 10 or more, and 21 at home and 13 in sanatorium had scores of 15 or more. Although the distributions are similar, there was a tendency for the home males to have slightly more cavitation, the mean score for cavitation being 12.27 for the home males and 10.80 for the sanatorium males. This difference is not statistically significant. Considering the females, 21 out of 33 at home had a score of 10 or more compared with 14 of 31 in sanatorium, and there were five at home with a score of 25 or more compared with none in sanatorium. The mean score for cavitation was 12.82 for the home females compared with 8.45 for the sana-

TABLE 5

EXTENT OF CAVITATION AND EXTENT OF DISEASE FOR THE PATIENTS IN THE MAIN ANALYSIS, AS ASSESSED ON A POSTERO-ANTERIOR RADIOGRAPH BEFORE TREATMENT BY TWO RADIOLOGICAL ASSESSORS, USING DIFFERENT METHODS

Extent of cavitation														Extent of disease													
grading method (Dr Ida B. Scudder)							scoring method (Dr J. Frimodt-Møller)							lung zones involved in disease (Dr Ida B. Scudder)							total extent of disease and cavitation (Dr J. Frimodt-Møller)						
grading	number of patients						score	number of patients						number	number of patients						score	number of patients					
	home			sanatorium				home			sanatorium				home			sanatorium				home			sanatorium		
	M	F	T	M	F	T		M	F	T	M	F	T		M	F	T	M	F	T		M	F	T	M	F	T
							0	7	1	8	4	3	7	1	1	1	2	0	0	0	1-9	0	1	1	2	0	2
Nil	6	3	9	5	2	7	1-4	3	2	5	5	1	6								10-19	2	1	3	4	2	6
							5-9	11	9	20	14	13	27	2	6	1	7	10	2	12	20-29	10	4	14	9	5	14
Slight	7	2	9	13	4	17															30-39	5	2	7	4	6	10
							10-14	7	10	17	14	7	21	3	4	4	8	8	6	14	40-49	4	7	11	5	8	13
							15-19	9	6	15	2	5	7								50-59	6	6	12	11	6	17
Moderate	17	9	26	16	18	34								4	11	9	20	13	11	24	60-69	6	4	10	4	3	7
							20-24	7	0	7	5	2	7								70-79	10	3	13	2	0	2
							25-29	1	2	3	5	0	5	5	13	9	22	10	4	14	80-89	1	1	2	5	1	6
Extensive	19	19	38	16	7	23															90-99	2	2	4	4	0	4
							30 or more	4	3	7	1	0	1														
														6	14	9	23	9	8	17	100 or more	3	2	5	0	0	0
Total	49	33	82	50	31	81	Total	49	33	82	50	31	81	Total	49	33	82	50	31	81	Total	49	33	82	50	31	81

M = Male; F = Female; T = Total

torium females, a statistically significant difference. Thus, both approaches confirm that the home females were at a definite disadvantage in respect of cavitation.

As regards the total extent of disease, the distributions for the males were similar, though the mean score was 54.08 for the home males and 48.26 for the sanatorium males, so that again the home males were at some disadvantage, although the difference does not attain statistical significance. For the females, however, the distributions are substantially different. Thus, 12 at home had a score of 60 or more compared with four in sanatorium. The mean score was 53.79 for the home females and 41.81 for the sanatorium females, this difference being statistically significant. Again both approaches confirm that the home females were at a definite disadvantage in respect of total extent of disease.

Table 6 contains a summary of the cavitation findings and the findings on extent of disease by the two approaches, together with the percentage of patients with a 3-plus (heavy) positive direct smear. Comparing the home and sanatorium males first, although the former were at a disadvantage on each assessment, none of the differences attains statistical significance. On the other hand, when the home and sanatorium females are compared, the home females were not only at a disadvantage on each assessment, but the differences in respect of extensive cavitation, the mean score for cavitation and the mean score for total extent of disease, all attained statistical significance. It must be concluded that, despite randomization, the home and sanatorium series were not equivalent in several important factors at the start of treatment, but that the differences in the males were less than those in the females.

PLAN OF THE PRESENT REPORT

Because of the classification of patients into a main analysis group and several subsidiary groups, and because of the pretreatment differences between the home and sanatorium series, this report follows a rather complex plan. Section V contains a comparison of the progress of the males in the main analysis at home and in sanatorium. Section VI summarizes a similar comparison for the females in the main analysis. Section VII reports special analyses which were undertaken to investigate the bearing on the results of the pretreatment differences between the series. Section VIII illustrates the prognostic importance of various clinical characteristics at the start of treatment, for all the patients in the main analysis. Certain additional bacteriological findings for patients in the main analysis, for which it was not important to consider the sexes separately, are presented in section IX. An analysis of toxicity and other clinical complications of treatment for the entire group of 193 patients is given in section X. Sections XI and XII deal, respectively, with the self-administration of the medicine and with important social factors relevant to treatment at home and in sanatorium. The findings for the subsidiary groups of patients not included in the main analysis are considered in section XIII This presentation of the results is followed by the discussion (section XIV) and the summary (section XV).

TABLE 6

SUMMARY OF THE IMPORTANT DIFFERENCES IN THE CONDITION OF PATIENTS ON ADMISSION TO TREATMENT

Sex	Treatment series	Number of patients in main analysis	Extent of cavitation		Extent of disease		% with 3-plus (heavy) direct smear
			% with extensive cavitation	mean score for cavitation	% with five or six lung zones involved	mean score for total extent	
Male	Home	49	*39*	12.27	*55*	54.08	*59*
	Sanatorium	50	*32*	10.80	*38*	48.26	*44*
Female	Home	33	*58*	12.82	*55*	53.79	*45*
	Sanatorium	31	*23*	8.45	*39*	41.81	*26*

V. COMPARISON OF HOME AND SANATORIUM TREATMENT IN MALES

CLINICAL

Deaths

There were three deaths in the 99 male patients in the main analysis during the 12-month period, two among the 49 males in the home series and one among the 50 males in sanatorium. One of the home patients died of tuberculosis in the eighth week of treatment. He had been in poor general condition from the start, with severe albuminuria, and failed to respond clinically, although at the end of one month there was some evidence of a bacteriological response. Thus, the results of two cultures of collection specimens of sputum before treatment were " confluent growth " and " 100-20 colonies ", but at one month the cultures from two collection specimens grew 10 and two colonies respectively. The second death in a home male was non-tuberculous. A patient who was making good progress and who had returned to part-time activity took a temporary job in the seventh month of treatment and was electrocuted whilst at work. All 13 of the bacteriological specimens which were cultured from the second month onwards were negative. A post-mortem examination showed no evidence of active tuberculosis. The sanatorium death, which was due to tuberculosis, occurred after 14 days of treatment.

Change of chemotherapy

The progress of one male patient at home was sufficiently unsatisfactory bacteriologically and radiographically for it to be felt before the end of the 12-month period that it was unjustifiable for the patient to continue on the prescribed chemotherapy. He had shown an early response to treatment, both radiographic and bacteriological. At two months the two available cultures were negative, and so were the four cultures at three months and the three at four months. At five months one of the three cultures was positive, yielding two colonies resistant to isoniazid but sensitive to PAS, and at six months one of two cultures yielded eight colonies with a similar resistance pattern. By seven months the sputum had become positive again on direct smear examination, and by nine months the organisms were resistant to PAS as well as to isoniazid ; the disease, which had been improving for the first months, then showed definite radiographic deterioration. Chemotherapy was changed at the end of nine months to streptomycin plus pyrazinamide, and the nine cultures at 10, 11 and 12 months were all negative. On admission to treatment, this patient had an acute moderately extensive unilateral lesion with a small dorsal lobe cavity. He was co-operative and, as far as is known, took his cachets regularly.

In addition to this change of chemotherapy, and modifications in one home and two sanatorium males during desensitization to PAS, there were three home patients, each of whom left Madras for a week without informing the Centre and so without taking a supply of medicine. Another patient had no chemotherapy for the last 18 days of the 12 months, because of dysphagia due to a carcinoma of the oesophagus. In sanatorium, two patients who were discharged and then readmitted had interruptions of chemotherapy for one week and one month respectively. Because these interruptions represented only a small proportion of the 12-month period of treatment, the patients concerned were retained in the main analysis.

Weight changes

The weight changes for the 12-month period are set out in Table 7. During the first six months all except three (6%) of the 47 home males, and all of the 49 sanatorium males, gained weight. Whereas 30% of the home males gained at least 14 lb. (6.4 kg), the corresponding figure for the sanatorium males was 65%. The average gain in weight was 10.0 lb. (4.5 kg) for the home males and 16.6 lb. (7.5 kg) for those in sanatorium. The difference in average weight gain is statistically significant at the 0.1% level. In the second six months many patients in both series lost weight. Thus 50% of the 44 home and 33% of the 49 sanatorium patients lost some weight, but none as much as 7 lb. (3.2 kg). Even so, there was still a slight increase in the average weights—namely, 0.8 lb. (0.36 kg) for the home males and 1.2 lb. (0.54 kg) for the sanatorium males. Finally, considering the full 12-month period, 38% of 45 home and 69% of 49 sanatorium patients gained 14 lb. (6.3 kg) or more in weight, the average gains being 10.6 lb. (4.75 kg) and 17.8 lb. (8 kg) respectively for the two series. It may be concluded that although patients in both series gained weight

TABLE 7

WEIGHT CHANGES IN MALE PATIENTS IN THE 12-MONTH PERIOD

Period	Treatment series	Total male patients weighed		Weight gain								No change		Weight loss				Average gain in weight per patient (lb.)
				21 lb.* or more		14-20 lb.		7-13 lb.		less than 7 lb.				less than 7 lb.		7 lb. or more		
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
0-6 months **	Home	47	100	2	4	12	26	18	38	12	26	2	4	1	2	0	0	10.0
	San.	49	100	10	20	22	45	14	29	3	6	0	0	0	0	0	0	16.6
6-12 months †	Home	44	100	0	0	0	0	7	16	10	23	5	11	22	50	0	0	0.8
	San.	49	100	0	0	1	2	4	8	17	35	11	22	16	33	0	0	1.2
0-12 months ††	Home	45	99	6	13	11	24	12	27	14	31	1	2	1	2	0	0	10.6
	San.	49	100	15	31	19	39	11	22	4	8	0	0	0	0	0	0	17.8

* 1 lb. = 0.45 kg

** No result is available for two home patients (one died and one observation was missing), and for one sanatorium patient, who died.

† No result is available for five home patients (two died, one deteriorated and had his chemotherapy changed, one had a carcinoma of the oesophagus and one observation was missing), and for one sanatorium patient, who died.

†† No result is available for four home patients (two died, one deteriorated and had his chemotherapy changed, and one had a carcinoma of the oesophagus), and for one sanatorium patient, who died.

throughout the 12 months, there was a clear-cut benefit to the sanatorium series. In each series the greater part of the increase in weight occurred in the first six months.

Erythrocyte sedimentation rate

The distributions of the ESR at the start of treatment, at six months and at 12 months are set out in Table 8. Both series show a progressive decline in the number of patients with a high ESR. Thus, whereas only one patient in each series had an ESR of less than 20 before treatment, the corresponding figures were 15 for the home males and 27 for the sanatorium males at six months, and 21 and 29 respectively at 12 months. Six home compared with 23 sanatorium patients had an ESR within normal limits at 12 months. This difference is statistically significant at the 0.1% level. Many patients in both series still had an elevated ESR at 12 months, there being 24 home and 20 sanatorium patients with an ESR of more than 20. It may be concluded that in both series the ESR fell, and that the sanatorium series was at an advantage.

At the end of 12 months, patients were classified on the basis of their bacteriological results during the period into those bacteriologically quiescent, of doubtful status, relapsed or active (see page 77). The distribution of the ESR at 12 months in the 38 home and 41 sanatorium patients considered to have attained bacteriological quiescence at that time

TABLE 8

DISTRIBUTIONS OF THE ERYTHROCYTE SEDIMENTATION RATE IN MALE PATIENTS BEFORE TREATMENT, AT 6 AND AT 12 MONTHS

ESR (mm in 1 hr)	Before		At 6 months		At 12 months	
	home	san.	home	san.	home	san.
0- 10	1	1	7	16	6	23
11- 20	0	0	8	11	15	6
21- 50	9	8	20	13	16	12
51-100	30	27	12	8	8	8
101 or more	8	13	1	1	0	0
Total male patients assessed *	48	49	48	49	45	49

* Excluding throughout one home and one sanatorium patient who died in the first six months ; excluding also three home patients at 12 months only (one died in the second six months, one deteriorated and had his chemotherapy changed and for one the result was not available)

TABLE 9
DISTRIBUTION OF THE ERYTHROCYTE SEDIMENTATION RATE IN MALE PATIENTS WITH BACTERIOLOGICALLY QUIESCENT DISEASE AT THE END OF 12 MONTHS

ESR (mm in 1 hr)	Home		Sanatorium	
	number	%	number	%
0- 10	5	*13*	21	*51*
11- 20	12	*32*	5	*12*
21- 50	15	*39*	9	*22*
51-100	6	*16*	6	*15*
Total	38	*100*	41	*100*

is given in Table 9. It can be seen that 55% of the home and 37% of the sanatorium patients who had attained bacteriological quiescence still had an ESR of more than 20. It may be concluded that an elevated ESR is quite compatible with bacteriological quiescence, as defined in this report. It is of interest, however, that the proportion of patients with an elevated ESR associated with bacteriologically quiescent disease was greater in the home than in the sanatorium series. Further studies are being undertaken to investigate whether an elevated ESR indicates persisting activity in the lesion or whether there are other reasons for the elevation as, for example, in many patients in East Africa (Courdurier & Brygoo, 1947 ; McGregor & Deegan, 1954).

Radiographic changes

The changes in the radiographic appearances were assessed by a radiological assessor, Dr Ida B. Scudder, who was unaware to which series any patient had been allocated. Four grades of improvement were used— namely, exceptional, considerable, moderate and slight—and three of deterioration—slight, moderate and considerable. The three radiographs assessed—namely, those taken before treatment, at six and at 12 months—had all been taken at the Chemotherapy Centre, so that the radiographic techniques were similar for the two series. The assessor carried out three completely separate assessments. First she was shown the pretreatment and six-month radiographs, the patients in the two series being considered in a random order, and she made an assessment of progress for the first six months. When this assessment was complete for all the patients in both series, a similar assessment was made for the 12-month period, the assessor being shown the pretreatment and the 12-month radiographs of each patient. Finally, the radiographs at six and 12 months were viewed and the changes in the second six months were assessed. The same grades were used for radiographic changes for each of the three assessments. It will be appreciated that the changes reported separately for the first six months and for the second six months do not always agree, when combined, with the change reported over the period of 12 months.

The findings for the males are set out in Table 10. Considering the changes over the first six-month period, it will be seen that the majority of patients in both series improved, 78% of 49 home and 68% of 50 sanatorium males showing moderate or greater improvement. No patient deteriorated and there was one death in each series. Considering the changes for the full 12 months, 73% of the home and 92% of the sanatorium patients showed moderate or greater improvement. During the second six months one home patient deteriorated and his chemotherapy was changed. Although the sanatorium patients fared rather better, none of the differences attains statistical significance.

The radiographic changes in the second six months were very much slighter than those in the first six months, and were correspondingly much more difficult to assess. Of the 48 home males 23%, compared with 37% of the 49 sanatorium patients, showed slight radiographic improvement ; only one patient (sanatorium) showed moderate improvement. Whereas there were no deteriorations or deaths in the sanatorium series, there were two deteriorations and one change of chemotherapy in addition to a non-tuberculous death in the home series. Thus the sanatorium series showed a greater benefit than the home series in the second six months, though the changes observed were radiographically minor. There was also a slight tendency for deterioration to occur in this period in the home series.

In summary, there was little to choose between the two series in the first six months. However, in the second six months and over the whole 12 months the sanatorium males fared rather better than the home males.

Changes in cavitation

Table 11 presents the changes in cavitation for the 12-month period, as assessed by Dr Ida B. Scudder. For this assessment a single postero-anterior radiograph taken before the start of treat-

TABLE 10

CHANGES IN THE RADIOGRAPHIC APPEARANCES IN MALE PATIENTS IN THE 12-MONTH PERIOD

Period *	Treatment series	Total male patients		Improvement								No change		Deterioration				Change of chemotherapy after deterioration		Death	
				exceptional		considerable		moderate		slight				slight		moderate					
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0-6 months	Home	49	99	2	4	12	24	24	49	8	16	2	4	0	0	0	0	0	0	1	2
	Sanatorium	50	100	1	2	16	32	17	34	13	26	2	4	0	0	0	0	0	0	1	2
0-12 months	Home	49	100	2	4	17	35	17	35	10	20	0	0	0	0	0	0	1	2	2**	4
	Sanatorium	50	100	0	0	25	50	21	42	3	6	0	0	0	0	0	0	0	0	1	2
6-12 months	Home	48	100	0	0	0	0	0	0	11	23	33	69	2	4	0	0	1	2	1†	2
	Sanatorium	49	100	0	0	0	0	1	2	18	37	30	61	0	0	0	0	0	0	0	0

* Three separate assessments on standard radiographs ** Including one non-tuberculous death
† A non-tuberculous death

ment was used to classify cavitation on admission, but at 12 months both a standard radiograph and a series of tomograms were used to assess the extent of any residual cavitation. Of the 40 home males and 44 in sanatorium with initial cavitation, all except two at home and one in sanatorium had no cavitation or less cavitation at 12 months. In 38% of the home and in 50% of the sanatorium patients cavitation had disappeared and in 58% of the home and 48% of the sanatorium patients there

TABLE 11

CHANGES IN CAVITATION IN THE 12-MONTH PERIOD IN MALE PATIENTS WITH CAVITATION BEFORE TREATMENT, ACCORDING TO ITS EXTENT BEFORE TREATMENT *

Extent of cavitation before treatment	Treatment series	Total male patients		Disappearance of cavitation		Cavities smaller or fewer		No change		Cavities larger or more numerous	
		number	%	number	%	number	%	number	%	number	%
Extensive	Home	18	101	1	(6)**	16	(89)	1	(6)	0	(0)
	Sanatorium	15	101	4	(27)	10	(67)	1	(7)	0	(0)
Moderate	Home	15	100	8	(53)	6	(40)	1	(7)	0	(0)
	Sanatorium	16	100	7	(44)	9	(56)	0	(0)	0	(0)
Slight	Home	7	100	6	(86)	1	(14)	0	(0)	0	(0)
	Sanatorium	13	100	11	(85)	2	(15)	0	(0)	0	(0)
Total male patients with cavitation †	Home	40	101	15	38	23	58	2	5	0	0
	Sanatorium	44	100	22	50	21	48	1	2	0	0

* Assessment on a standard radiograph before treatment, and a standard radiograph and tomograms at 12 months
** Percentages based on fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.
† Excluding three home patients (two died and one deteriorated and had his chemotherapy changed) and one sanatorium patient who died

was less cavitation. It is of importance to note that in each series the cavities closed in a much higher proportion of the patients with slight or moderate cavitation than of the patients with extensive cavitation. Thus, six of seven home and 11 of 13 sanatorium patients with slight cavitation achieved cavity closure, compared with only one of 18 home and four of 15 sanatorium patients with extensive cavitation ; the findings for patients with moderate cavitation were intermediate. There were six home and five sanatorium patients with no cavitation visible before treatment. At 12 months one of these in each series had slight cavitation.

Summary of the clinical comparison

At the end of 12 months the sanatorium males had gained more weight and had lower ESRs, and both these differences between the series attain statistical significance. However, the weight differences are undoubtedly influenced by the differences in diet and rest (section XII, page 106 et seq.) and may be unrelated to the progress of the disease as such; and, as already suggested, the ESR is probably subject to influences other than the tuberculous disease. There was comparatively little to choose between the two series in the radiographic findings, whether expressed in terms of over-all radiographic changes or changes in cavitation, though the sanatorium males fared slightly better in terms of radiographic improvement in the second six months, and rather better over the whole 12 months. Furthermore, in judging the extent even of these radiographic differences, it must be recalled that the home males were at a radiographic and bacteriological disadvantage before treatment; when allowance is made for the pretreatment differences (section VII) the progress of the two series shows an even closer similarity.

BACTERIOLOGICAL

Smear and culture results

The bacterial content of the sputum was studied by direct smear examination and by culture before the start of treatment and monthly thereafter, usually on several specimens at the end of each month. The results of the smear and culture examinations of *single* collection specimens of sputum each month for the male patients are set out for the 12-month period in Table 12 (see also Fig. 1). This table,

FIG. 1
PERCENTAGE OF PATIENTS EACH MONTH WITH A POSITIVE CULTURE RESULT FROM A SINGLE COLLECTION SPECIMEN OF SPUTUM

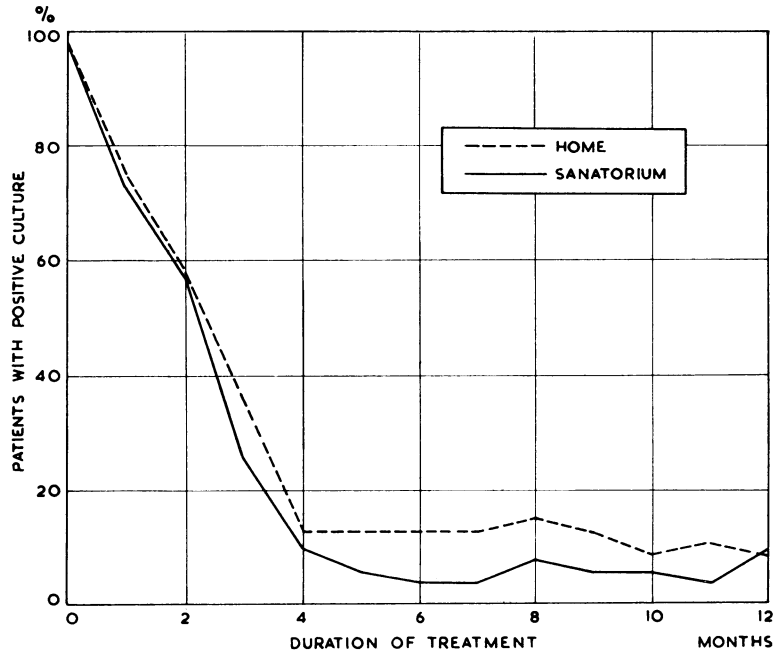

TABLE 12

PRESENCE OF TUBERCLE BACILLI IN MALE PATIENTS IN SINGLE COLLECTION SPECIMENS OF SPUTUM TAKEN AT MONTHLY INTERVALS

Months after start of chemotherapy	Treatment series	Total patients tested	Culture positive									Culture negative *	
			total patients positive on culture		smear positive, graded as :			smear negative, culture graded as :					
			number	%	3-plus	2-plus	1-plus	3-plus	2-plus	1-plus	19-1 colonies	number	%
0	Home	49	48	*98*	30	11	4	0	0	0	3	1	*2*
	Sanatorium	49	48	*98*	22	10	9	1	0	3	3	1	*2*
1	Home	44	33	*75*	1	10	14	0	1	3	4	11	*25*
	Sanatorium	49	36	*73*	1	7	15	0	1	6	6	13	*27*
2	Home	48	28	*58*	1	3	12	0	0	4	8	20	*42*
	Sanatorium	49	28	*57*	0	3	10	0	0	5	10	21	*43*
3	Home	47	17	*36*	0	2	5	0	0	2	8	30	*64*
	Sanatorium	47	12	*26*	0	0	4	0	0	2	6	35	*74*
4	Home	48	6	*13*	0	1	0	0	1	0	4	42	*88*
	Sanatorium	49	5	*10*	0	0	1	0	1	1	2	44	*90*
5	Home	48	6	*13*	0	0	3	0	0	1	2	42	*88*
	Sanatorium	49	3	*6*	0	0	0	0	0	2	1	46	*94*
6	Home	48	6	*13*	0	0	3	0	0	1	2	42	*88*
	Sanatorium	48	2	*4*	0	0	0	0	0	1	1	46	*96*
7	Home	46	6	*13*	0	2	2	0	0	1	1	40	*87*
	Sanatorium	49	2	*4*	0	0	1	0	0	0	1	47	*96*
8	Home	46	7	*15*	0	5	0	0	0	0	2	39	*85*
	Sanatorium	49	4	*8*	0	0	1	0	0	3	0	45	*92*
9	Home	45	6	*13*	1	2	2	0	0	0	1	39	*87*
	Sanatorium	48	3	*6*	0	1	1	0	0	0	1	45	*94*
10	Home	45 **	4	*9*	1	2	1	0	0	0	0	41	*91*
	Sanatorium	48	3	*6*	1	0	1	0	0	0	1	45	*94*
11	Home	45 **	5	*11*	0	2	2	0	0	0	1	40	*89*
	Sanatorium	48	2	*4*	1	0	0	0	0	0	1	46	*96*
12	Home	44 **	4	*9*	0	1	3	0	0	0	0	40	*91*
	Sanatorium	48	5	*10*	0	2	1	0	0	1	1	43	*90*

* Even if the smear was positive (see page 73)

** Excluding one patient who deteriorated and had his chemotherapy changed (see page 67)

being based on single monthly cultures, a usual rhythm of investigation of tuberculous patients under active treatment, is readily comparable with the findings of other studies. Further investigation, reported in section IX below, suggests that the bacilli in smear-positive culture-negative specimens were non-viable; it has therefore been considered justifiable to regard these results as bacteriologically negative. It will be noted that in the final column of this table, smear-positive culture-negative results are included with those negative both on smear and on culture.

It will be seen that in the early months there was a rapid decline in the number of patients with positive cultures, and by four months only six (13%) of 48 home and five (10%) of 49 sanatorium patients yielded positive cultures. The proportions of patients with positive results, both at home and in sanatorium, altered very little throughout the rest of the 12 months. At 12 months, four (9%) of 44 home patients were bacteriologically positive (and a fifth patient had deteriorated and had his chemotherapy changed), compared with five (10%) of 48 males in sanatorium. Considering the grading of sputum positivity, it will be seen that before the start of treatment the specimens of the great majority of patients were positive on smear, and that there was a rapid decline in positivity in the first three months, which was maintained throughout the rest of the 12 months. It may be concluded that both series showed a rapid and striking fall both in the number of patients positive on a single collection specimen and in the degree of positivity, and that there was little difference between the two series.

The multiple specimens that were examined at monthly intervals have already been described (see page 58). The findings for these *multiple* specimens at each of the 12 months are set out in Table 13 (see also Fig. 2). This table shows the findings both in terms of *patients tested* and in terms of *specimens examined.* It should be noted that in this table, as in Table 12, smear-positive culture-negative results have been included with the smear-negative culture-negative results.

From the right-hand section of Table 13 headed " Specimens examined " it will be seen that the average number of specimens per patient was very similar for the two series at each month, being about

FIG. 2
PERCENTAGE OF PATIENTS EACH MONTH WITH AT LEAST ONE POSITIVE CULTURE RESULT FROM MULTIPLE BACTERIOLOGICAL SPECIMENS (SPUTUM AND LARYNGEAL SWABS)

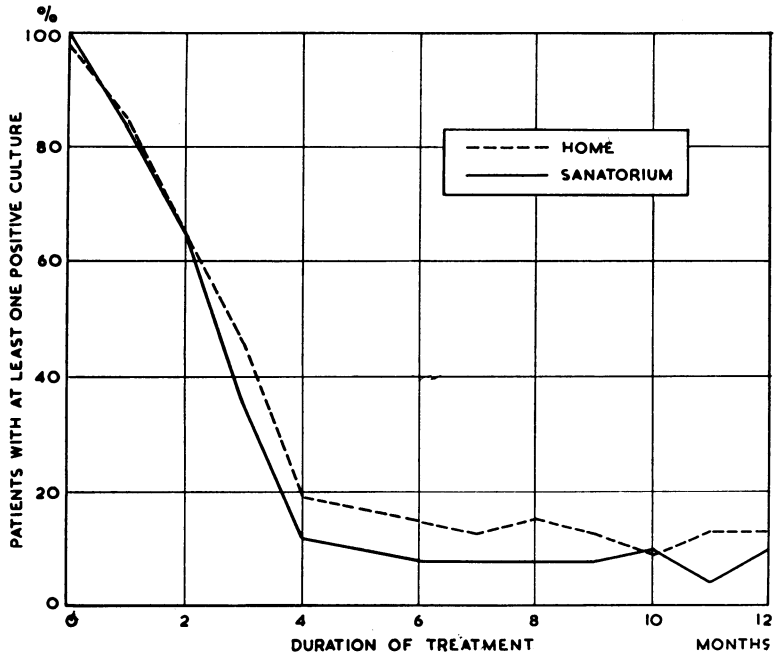

TABLE 13

PRESENCE OF TUBERCLE BACILLI IN MALE PATIENTS IN MULTIPLE SPECIMENS TAKEN AT MONTHLY INTERVALS

Months after start of chemotherapy	Treatment series	Patients tested												Specimens examined							
		total patients with results of at least one complete test available* (a)	total patients positive on culture on at least one test		highest grade of positivity on smear for each patient with at least one smear-positive culture-positive result			highest grade of positivity on culture for each patient with no smear-positive culture-positive result				total patients negative on all cultures **		total specimens examined (b)	average number of specimens per patient	culture positive					culture negative **	
			No.	% of (a)	3-plus	2-plus	1-plus	3-plus	2-plus	1-plus	19-1 colonies	No.	% of (a)			total positive cultures		smear positive	smear negative	laryngeal swab	No.	% of (b)
																No.	% of (b)					
0	Home	48	47	*98*	31	10	3	0	0	0	3	1	*2*	179	3.7	172	*96*	153	19	—	7	*4*
	Sanatorium	49	49	*100*	31	10	3	0	1	2	2	0	*0*	181	3.7	167	*92*	134	33	—	14	*8*
1	Home	47	40	*85*	2	15	11	0	1	2	9	7	*15*	117	2.5	86	*74*	54	32	—	31	*26*
	Sanatorium	49	41	*84*	3	10	15	0	0	7	6	8	*16*	117	2.4	88	*75*	50	38	—	29	*25*
2	Home	48	31	*65*	1	7	11	0	1	5	6	17	*35*	122	2.5	67	*55*	36	31	—	55	*45*
	Sanatorium	49	32	*65*	0	6	8	0	1	4	13	17	*35*	123	2.5	63	*51*	25	38	—	60	*49*
3	Home	48	22	*46*	0	3	9	0	0	2	8	26	*54*	142	3.0	39	*27*	16	21	2	103	*73*
	Sanatorium	49	17	*35*	0	1	4	0	0	4	8	32	*65*	141	2.9	24	*17*	7	17	0	117	*83*
4	Home	48	9	*19*	0	2	3	0	1	0	3	39	*81*	142	3.0	15	*11*	6	8	1	127	*89*
	Sanatorium	49	6	*12*	0	0	2	0	1	0	3	43	*88*	153	3.1	11	*7*	3	7	1	142	*93*
5	Home	48	8	*17*	0	0	3	0	0	1	4	40	*83*	152	3.2	13	*9*	3	10	0	139	*91*
	Sanatorium	49	5	*10*	0	0	1	0	0	3	1	44	*90*	152	3.1	8	*5*	1	6	1	144	*95*
6	Home	48	7	*15*	0	1	2	0	0	1	3	41	*85*	148	3.1	13	*9*	5	7	1	135	*91*
	Sanatorium	49	4	*8*	0	0	1	0	0	2	1	45	*92*	158	3.2	6	*4*	1	5	0	152	*96*
7	Home	47	6	*13*	0	2	3	0	0	0	1	41	*87*	145	3.1	12	*8*	6	4	2	133	*92*
	Sanatorium	49	4	*8*	0	0	1	0	0	2	1	45	*92*	157	3.2	6	*4*	2	3	1	151	*96*
8	Home	46	7	*15*	2	3	1	0	0	0	1	39	*85*	138	3.0	15	*11*	11	2	2	123	*89*
	Sanatorium	49	4	*8*	0	0	1	0	0	3	0	45	*92*	153	3.1	8	*5*	1	6	1	145	*95*
9	Home	47	6	*13*	1	4	0	0	0	0	1	41	*87*	133	2.8	13	*10*	10	2	1	120	*90*
	Sanatorium	49	4	*8*	0	1	1	0	0	1	1	45	*92*	144	2.9	8	*6*	4	3	1	136	*94*
10	Home	46 †	4	*9*	1	2	1	0	0	0	0	42	*91*	132	2.9	11	*8*	8	1	2	121	*92*
	Sanatorium	49	5	*10*	1	0	1	0	0	0	3	44	*90*	149	3.0	8	*5*	4	2	2	141	*95*
11	Home	46 †	6	*13*	1	2	1	0	0	0	2	40	*87*	131	2.8	11	*8*	7	2	2	120	*92*
	Sanatorium	49	2	*4*	1	0	0	0	0	1	0	47	*96*	137	2.8	4	*3*	2	2	0	133	*97*
12	Home	46 †	6	*13*	0	1	3	0	0	1	1	40	*87*	119	2.6	12	*10*	7	2	3	107	*90*
	Sanatorium	49	5	*10*	0	2	2	0	0	0	1	44	*90*	141	2.9	11	*8*	6	2	3	130	*92*

* For definition of complete test, see page 59. ** Even if the smear was positive (see page 73)

† Excluding one patient who deteriorated and had his chemotherapy changed (see page 67)

three for each examination. The pretreatment average was higher—namely, 3.7 in each series—and the averages at one and two months were lower, since only two specimens were examined at these months in the later stages of the study (see page 58). In interpreting the findings presented in the table it is important to remember the intensity of bacteriological investigation of both series, which is believed to be greater than in any other large-scale controlled clinical trial so far reported. It will also be appreciated that the percentages of patients with positive cultures provide a valid comparison between home and sanatorium patients at each month, because of the close similarity in the average number of tests per patient, but not strictly from month to month, since both the average and the type of specimen vary. Even so, the trends revealed by the figures are so striking that there can be no doubt of their validity.

Considering the patients tested (left-hand section of Table 13), there was a progressive and rapid fall in both series in the percentage of patients with positive cultures. At four months only 19% of 48 home patients and 12% of 49 sanatorium patients yielded positive cultures. At six months there was a further slight decline, to 15% of 48 home patients and 8% of 49 sanatorium patients, but thereafter there was no major change for the rest of the 12-month period. At 12 months, six (13%) of 46 home patients, compared with five (10%) of 49 sanatorium patients, yielded positive cultures. In addition, one home patient had deteriorated and had his chemotherapy changed. None of the differences between the series attains statistical significance.

Considering the highest grade of positivity on smear for those patients with positive cultures, it can be seen that in the early months there was a rapid decline in the grading of the positive smears; for example, at five months the three positive smears from the home series and the one positive smear from the sanatorium series were all graded as 1-plus. In the later months, although the figures are small, there was a tendency to find higher gradings in both series.

Considering the findings for all the specimens examined (right-hand section of Table 13), it will be seen that the percentages of specimens negative on culture were similar in the two series, though there was a tendency for the percentages to be slightly larger for the sanatorium patients each month.

It may be concluded that the results for the multiple specimens confirmed the results of single collection specimens in showing a striking decline in infectivity, which was slightly greater in the sanatorium series. But again it will be recalled that there was a radiographic and bacteriological disadvantage to the home males before treatment, which is, at least in part, responsible for the difference in the bacteriological findings (section VII).

It is of interest to compare Table 13 with Table 12 to see what additional information was obtained from the multiple specimens. The most important advantages were that more positive cultures were obtained for sensitivity testing and that the multiple tests permitted a firmer diagnosis of bacteriological quiescence (see page 77) than would have been possible on single monthly cultures. Apart from these, the gains are relatively small. The number of patients for whom results were available each month was slightly higher in Table 13. The total number of patients who yielded positive cultures was also higher; for example, at three months 22 of the home and 17 of the sanatorium patients yielded positive results from the multiple specimens, compared with 17 of the home and 12 of the sanatorium patients from the single collection specimens. At six months the corresponding figures were seven and four for the multiple specimens and six and two for the single specimens. At 12 months the figures were six for the home and five for the sanatorium from multiple specimens, compared with four for the home and five for the sanatorium from the single specimens.

Isoniazid sensitivity [1]

The results of the isoniazid-sensitivity tests for male patients are set out in Table 14. At three months there were 21 cultures tested from 48 males at home, of which one was resistant, compared with one resistant strain among 18 cultures tested from 49 patients in sanatorium. Thereafter, the number of resistant strains increased month by month and at six months five of seven strains in the home series were resistant compared with all the four strains in the sanatorium series. In the second six months the majority of the positive cultures were resistant, but it will be seen that even at 12 months sensitive strains were obtained from some patients in each series—

[1] Because of certain difficulties in the interpretation of PAS-sensitivity tests in Indian patients, it was desirable to present all the information on PAS sensitivity together, in one section of this report. The results of the monthly sensitivity tests will be found in section IX (page 95).

TABLE 14

RESULTS OF ISONIAZID-SENSITIVITY TESTS IN MALE PATIENTS TREATED WITH ISONIAZID PLUS PAS FOR A PERIOD OF 12 MONTHS *

Months after start of chemotherapy	Treatment series	Total patients with cultures examined (a)	Culture-negative (no sensitivity test possible)	Culture-positive but no sensitivity result available	Patients culture-positive with sensitivity tests								
					total results available (b)	sensitive	resistant				total resistant to isoniazid		
						no growth on 0.2 μg/ml	growth on 0.2 μg/ml, not on 1, repeated	growth on 1 μg/ml, not on 5	growth on 5 μg/ml, not on 50	growth on 50 μg/ml	number	% of (b)	% of (a)
1	Home	48	7	1	40	40	0	0	0	0	0	*0*	*0*
	Sanatorium	49	8	3	38	38	0	0	0	0	0	*0*	*0*
2	Home	48	17	1	30	29	0	1	0	0	1	*3*	*2*
	Sanatorium	48	17	2	29	29	0	0	0	0	0	*0*	*0*
3	Home	48	26	1	21	20	1	0	0	0	1	*(5)***	*2*
	Sanatorium	49	30	1	18	17	1	0	0	0	1	*(6)*	*2*
4	Home	48	39	0	9	6	0	3	0	0	3	*(33)*	*6*
	Sanatorium	49	43	0	6	5	1	0	0	0	1	*(17)*	*2*
5	Home	48	40	0	8	3	0	3	0	2	5	*(63)*	*10*
	Sanatorium	49	44	0	5	1	2	0	1	1	4	*(80)*	*8*
6	Home	48	41	0	7	2	0	4	0	1	5	*(71)*	*10*
	Sanatorium	49	45	0	4	0	2	0	1	1	4	*(100)*	*8*
7	Home	47	41	0	6	0	0	5	0	1	6	*(100)*	*13*
	Sanatorium	49	45	1	3	0	1	0	1	1	3	*(100)*	*6*
8	Home	46	39	0	7	0	1	3	0	3	7	*(100)*	*15*
	Sanatorium	49	45	0	4	0	2	0	1†	1	4	*(100)*	*8*
9	Home	47	41	0	6	1	1	3	0	1	5	*(83)*	*11*
	Sanatorium	49	45	0	4	1	1	0	1	1	3	*(75)*	*6*
10	Home	46††	42	0	4	0	0	3	0	1	4	*(100)*	*9*
	Sanatorium	49	44	0	5	1	2	0	1†	1	4	*(80)*	*8*
11	Home	46††	40	0	6	0	1	3	0	2	6	*(100)*	*13*
	Sanatorium	49	47	0	2	0	2	0	0	0	2	*(100)*	*4*
12	Home	46††	40	0	6	2	1	1	1†	1	4	*(67)*	*9*
	Sanatorium	49	44	1	4	2	1	0	1	0	2	*(50)*	*4*

* All patients had strains sensitive to isoniazid and PAS before treatment.

** Percentages based on fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.

† No result on 50 μg/ml †† Excluding one patient who deteriorated and had his chemotherapy changed (see page 67)

namely, two of six strains in the home series and two of four strains in sanatorium.

Expressing the resistant results as a proportion of the total number of patients in whom cultures were examined, the figures were 2% for both groups at three months; at six months the corresponding percentages were 10% for the home and 8% for the sanatorium; at nine months they were 11% and 6% respectively, and at 12 months 9% and 4% respectively. Although the proportion of resistant strains was slightly higher in the home series, none of the differences attains statistical significance.

In summary, the proportion of positive strains which were resistant was higher in both groups in the later months of treatment, and the home series, which yielded a larger proportion of positive cultures, also yielded a larger total of resistant results.

Bacteriological status at the end of 12 months

Table 15 presents, for the male patients, a classification of the activity of the disease at 12 months, based on the results of cultures during the 12-month period. A patient's disease has been classified as bacteriologically quiescent if all the cultures for at least the last three monthly examinations (that is, those at 10, 11 and 12 months) were negative. Those patients who, following at least three months of culture negativity, yielded an isolated positive culture at one of the last three monthly examinations, have been classified as bacteriologically of doubtful status. Patients whose sputum was culture-positive on at least two occasions at the examinations for the last three months are classified as bacteriologically relapsed, if they had previously yielded only negative results for all the cultures at three consecutive monthly examinations. Patients who never had a period of three months of bacteriological negativity have been classified as bacteriologically active, as has the patient who had his chemotherapy changed because of a radiological spread, associated with a positive sputum (see page 67). It can be seen from Table 15 that the majority of patients in both groups—namely, 38 (78%) of 49 home and 41 (82%) of 50 sanatorium patients—attained bacteriological quiescence. The two series have fared very similarly. There was, however, a tendency for sputum conversion to occur earlier in the sanatorium males, and 28 (68%) of the 41 who attained quiescence had converted by three months compared with 19 (50%) of the 38 at home. Four (8%) home and three (6%) sanatorium patients were classified bacteriologically

TABLE 15

CLASSIFICATION OF DISEASE IN MALE PATIENTS AT THE END OF 12 MONTHS AS QUIESCENT, OF DOUBTFUL STATUS, RELAPSED OR ACTIVE ON THE BASIS OF CULTURE RESULTS DURING THE PERIOD

Bacteriological status at the end of 12 months	Home		Sanatorium	
	number	%	number	%
Patients bacteriologically quiescent: that is, patients whose cultures were all negative for at least the last three monthly examinations—i.e., at 10, 11 and 12 months				
First monthly examination at which all the cultures were negative and remained so:				
1	5		5	
2	8		10	
3	6		13	
4	11		11	
5	2		1	
6	1		0	
7	2		0	
8	0		1	
9	2		0	
10	1		0	
Total patients with bacteriologically quiescent disease at 12 months	38	*78*	41	*82*
Patients bacteriologically of doubtful status: that is, patients whose cultures were all negative at three or more consecutive monthly examinations, but who produced an isolated positive culture at one of the last three monthly examinations—i.e., at 10, 11 or 12 months	4	*8*	3	*6*
Patients bacteriologically relapsed: that is, patients whose cultures were all negative at three or more consecutive monthly examinations, but who produced two or more positive cultures in the last three monthly examinations—i.e., at 10, 11 and 12 months	0	*0*	1	*2*
Patients bacteriologically active: that is, (*a*) patients whose cultures were never all negative at three consecutive monthly examinations	4	*8*	4	*8*
or (*b*) patients who deteriorated and had their chemotherapy changed	1	*2*	0	*0*
Total patients with bacteriologically relapsed or active disease at 12 months	5	*10*	5	*10*
Deaths	2*	*4*	1	*2*
Total male patients	49	*100*	50	*100*

* Including one non-tuberculous death

as of doubtful status. Until the subsequent course of their disease is known it is uncertain whether these patients should be classed with the quiescent or with the active cases. None of the home patients and one in sanatorium relapsed bacteriologically. There were five home patients (including the one who deteriorated and had his chemotherapy changed) and four in sanatorium who were classified as bacteriologically active. There were in all, therefore, five (10%) home and five (10%) sanatorium patients with bacteriologically active disease at 12 months. It may be concluded that there was very little to choose between the two treatments, and that in each series the same proportion of patients had active disease after 12 months of treatment.

Summary of the bacteriological comparison

There was a striking decline in the bacterial content of the sputum in males, there being little to choose between the results in the two series. Resistance to isoniazid was also found with similar frequency in the two series; there were nevertheless some patients with positive cultures at 12 months, who still had organisms sensitive to isoniazid. In each series 10% of patients had bacteriologically active disease after 12 months of treatment.

VI. COMPARISON OF HOME AND SANATORIUM TREATMENT IN FEMALES

PRETREATMENT DIFFERENCES

It was pointed out in section IV that the two series of patients allocated to treatment at home and in sanatorium differed at the start of treatment in important radiographic and bacteriological respects, the disparities being greater for the females than for the males. In summary, the females at home were at a major disadvantage in respect of the extent of cavitation, in the total extent of disease radiographically, and in the bacterial content of the sputum. The differences in the assessments of cavitation and total extent of disease attained statistical significance. Thus, despite strict randomization, there were important differences between the females in the two series. In this section the findings for the females are given for the 12-month period, but they should be interpreted with great caution in view of the pretreatment differences just referred to. In section VII an examination is made of the extent to which the observed differences in the responses are likely to be due to the pretreatment differences.

TABLE 16

WEIGHT CHANGES IN FEMALE PATIENTS IN THE 12-MONTH PERIOD

Period	Treatment series	Total female patients weighed		Weight gain								No change		Weight loss				Average gain in weight per patient (lb.)
				21 lb.* or more		14-20 lb.		7-13 lb.		Less than 7 lb.				Less than 7 lb.		7 lb. or more		
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
0-6 months **	Home	27	100	2	7	8	30	14	52	3	11	0	0	0	0	0	0	11.7
	Sanatorium	30	101	11	37	11	37	5	17	3	10	0	0	0	0	0	0	17.7
6-12 months †	Home	25	100	0	0	0	0	2	8	11	44	2	8	7	28	3	12	0.0
	Sanatorium	30	100	0	0	2	7	15	50	8	27	0	0	4	13	1	3	6.2
0-12 months ††	Home	29	100	3	10	8	28	8	28	9	31	0	0	1	3	0	0	12.1
	Sanatorium	30	100	21	70	4	13	5	17	0	0	0	0	0	0	0	0	23.9

* 1 lb. = 0.45 kg

** No result is given for six home patients (who were pregnant), and for one sanatorium patient, who died.

† No result is given for eight home patients (one deteriorated and had her chemotherapy changed and seven were pregnant), and for one sanatorium patient, who died.

†† No result is given for four home patients (one deteriorated and had her chemotherapy changed and three were pregnant) and for one sanatorium patient, who died.

CLINICAL AND BACTERIOLOGICAL COMPARISON

Death

There was one death among the 64 females during the 12-month period. This occurred in a sanatorium patient who died of tuberculosis after five days of treatment.

Change of chemotherapy

The progress of one female patient at home, who had grossly extensive disease and cavitation before treatment, was sufficiently unsatisfactory for it to be felt, before the end of the 12-month period, that it was unjustifiable to continue with the prescribed chemotherapy. Although she showed an initial improvement in her general condition, she then slowly deteriorated clinically and radiographically. The sputum remained positive, and although the bacterial content was much reduced in the second and third months of treatment, the degree of positivity then increased. Isoniazid resistance emerged at three months and PAS resistance at five months. At 11 months chemotherapy was changed to streptomycin plus pyrazinamide. (The management of the patient was complicated by her domestic situation (she was deserted by her husband), and she was never very co-operative in her treatment.)

In addition to this change of chemotherapy, there were modifications of chemotherapy in three patients (two home, one sanatorium) during desensitization to PAS. One more patient had an interruption of chemotherapy; this was a female at home who visited her village without permission and so had no medicine for a week. Because these interruptions represented only a small proportion of the 12-month period of treatment the patients in question were retained in the main analysis.

Summary of the clinical comparison

The females in sanatorium gained more weight than the females at home, both in the first six months and in the second six months (Table 16). The ESR fell in both series but the sanatorium patients showed the greater benefit (Table 17). There was little to choose between the radiographic progress of the two series in the first six months, but in the second six months and over the whole 12-month period, the sanatorium patients made the greater progress (Table 18). Similarly, the proportion of patients with cavitation at the start of treatment which had disappeared at the end of 12 months was considerably higher for the sanatorium than for the home series (Table 19). This difference, however, was related to the fact that the proportion of patients with less extensive cavitation was higher in the sanatorium series than in the home series.

TABLE 17

DISTRIBUTIONS OF THE ERYTHROCYTE SEDIMENTATION RATE IN FEMALE PATIENTS BEFORE TREATMENT, AT 6 AND AT 12 MONTHS

ESR (mm in 1 hr)	Before		At 6 months		At 12 months	
	home	san.	home	san.	home	san.
0-10	0	1	1	6	3	5
11-20	0	2	4	7	3	9
21-50	3	3	14	16	17	15
51-100	21	15	13	1	9	1
101 or more	9	9	0	0	0	0
Total female patients assessed *	33	30	32	30	32	30

* Excluding throughout one sanatorium patient who died in the first six months ; excluding also one home patient at six months only (result not available) and one home patient at 12 months only (who deteriorated and had her chemotherapy changed).

Summary of the bacteriological comparison

There was a striking decline in the bacterial content of sputum in the females in both series, but the sanatorium series was at an advantage, especially in the later months. This same pattern was apparent whether single collection specimens (Table 20) or multiple specimens (Table 21) were compared. The isoniazid-sensitivity results followed the same pattern (Table 22) and the home series yielded more resistant strains than the sanatorium series throughout the 12 months. Considering the bacteriological status at the end of 12 months (Table 23), eight (24%) of 33 home patients had bacteriologically active disease, compared with one (3%) of 31 in sanatorium (and one death).

It may be concluded that the females in sanatorium fared better, both clinically and bacteriologically, when compared with those at home. In order to interpret these findings, however, it is essential to consider the influence of the pretreatment differences referred to above, and this is done in the next section.

TABLE 18

CHANGES IN THE RADIOGRAPHIC APPEARANCES IN FEMALE PATIENTS IN THE 12-MONTH PERIOD

Period *	Treatment series	Total female patients		Improvement								No change		Deterioration				Change of chemotherapy after deterioration		Death	
				exceptional		considerable		moderate		slight				slight		moderate					
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
0-6 months	Home	33	*99*	0	*0*	10	*30*	11	*33*	4	*12*	6	*18*	1	*3*	1	*3*	0	0	*0*	*3*
	Sanatorium	31	*100*	2	*6*	11	*35*	7	*23*	7	*23*	3	*10*	0	*0*	0	*0*	0	*0*	1	*0*
0-12 months	Home	33	*99*	1	*3*	13	*39*	8	*24*	8	*24*	1	*3*	0	*0*	1	*3*	1	*3*	0	*0*
	Sanatorium	31	*99*	1	*3*	15	*48*	9	*29*	4	*13*	1	*3*	0	*0*	0	*0*	0	*0*	1	*3*
6-12 months	Home	33	*100*	0	*0*	0	*0*	0	*0*	8	*24*	23	*70*	0	*0*	1	*3*	1	*3*	0	*0*
	Sanatorium	30	*100*	0	*0*	0	*0*	1	*3*	11	*37*	18	*60*	0	*0*	0	*0*	0	*0*	0	*0*

* Three separate assessments on standard radiographs

TABLE 19

CHANGES IN CAVITATION IN THE 12-MONTH PERIOD IN FEMALE PATIENTS WITH CAVITATION BEFORE TREATMENT, ACCORDING TO ITS EXTENT BEFORE TREATMENT *

Extent of cavitation before treatment	Treatment series	Total female patients		Disappearance of cavitation		Cavities smaller or fewer		No change		Cavities larger or more numerous	
		number	%	number	%	number	%	number	%	number	%
Extensive	Home	18	*101*	5	*(28)***	10	*(56)*	2	*(11)*	1	*(6)*
	Sanatorium	7	*100*	2	*(29)*	3	*(43)*	1	*(14)*	1	*(14)*
Moderate	Home	9	*100*	5	*(56)*	4	*(44)*	0	*(0)*	0	*(0)*
	Sanatorium	17	*100*	11	*(65)*	5	*(29)*	1	*(6)*	0	*(0)*
Slight	Home	2	*100*	1	*(50)*	1	*(50)*	0	*(0)*	0	*(0)*
	Sanatorium	4	*100*	4	*(100)*	0	*(0)*	0	*(0)*	0	*(0)*
Total female patients with cavitation †	Home	29	*100*	11	*38*	15	*52*	2	*7*	1	*3*
	Sanatorium	28	*101*	17	*61*	8	*29*	2	*7*	1	*4*

* Assessment on a pretreatment standard radiograph, and a standard radiograph and tomographs at 12 months
** Percentages based on fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.
† Excluding one home patient (who deteriorated and had her chemotherapy changed) and one sanatorium patient, who died

TABLE 20

PRESENCE OF TUBERCLE BACILLI IN FEMALE PATIENTS IN SINGLE COLLECTION SPECIMENS OF SPUTUM TAKEN AT THREE-MONTHLY INTERVALS

Months after start of chemotherapy	Treatment series	Total patients tested	Culture positive									Culture negative *	
			total patients positive on culture		smear positive, graded as :			smear negative, culture graded as :					
			number	%	3-plus	2-plus	1-plus	3-plus	2-plus	1-plus	19-1 colonies	number	%
0	Home	32	31	*97*	14	12	4	0	0	1	0	1	*3*
	Sanatorium	30	29	*97*	7	13	5	1	1	0	2	1	*3*
3	Home	33	9	*27*	0	0	4	0	0	2	3	24	*73*
	Sanatorium	29	4	*14*	0	0	2	0	0	2	0	25	*86*
6	Home	33	4	*12*	0	1	3	0	0	0	0	29	*88*
	Sanatorium	28	0	*0*	0	0	0	0	0	0	0	28	*100*
9	Home	33	3	*9*	2	0	0	0	0	0	1	30	*91*
	Sanatorium	28	0	*0*	0	0	0	0	0	0	0	28	*100*
12	Home	32 **	4	*13*	1	0	0	1	0	1	1	28	*88*
	Sanatorium	29	0	*0*	0	0	0	0	0	0	0	29	*100*

* Even if the smear was positive (see page 73)
** Excluding one patient who deteriorated and had her chemotherapy changed (see page 79)

TABLE 21

PRESENCE OF TUBERCLE BACILLI IN FEMALE PATIENTS IN MULTIPLE SPECIMENS TAKEN AT THREE-MONTHLY INTERVALS

Months after start of chemotherapy	Treatment series	Patients tested												Specimens examined							
		total patients with results of at least one complete test available* (a)	total patients positive on culture on at least one test		highest grade of positivity on smear for each patient with at least one smear-positive culture-positive result			highest grade of positivity on culture for each patient with no smear-positive culture-positive result				total patients negative on all cultures **		total specimens examined (b)	average number of specimens per patient	culture positive					culture negative**	
																total positive cultures		smear positive	smear negative	laryngeal swab		
			No.	% of (a)	3-plus	2-plus	1-plus	3-plus	2-plus	1-plus	19-1 colonies	No.	% of (a)			No.	% of (b)				No.	% of (b)
0	Home	33	33	*100*	17	14	1	0	0	1	0	0	*0*	125	3.8	120	*96*	104	16	—	5	*4*
	Sanatorium	30	29	*97*	15	10	3	0	0	0	1	1	*3*	114	3.8	103	*90*	85	18	—	11	*10*
3	Home	33	14	*42*	0	0	6	0	0	3	5	19	*58*	107	3.2	22	*21*	7	14	1	85	*79*
	Sanatorium	30	7	*23*	0	0	3	0	0	4	0	23	*77*	100	3.3	12	*12*	4	7	1	88	*88*
6	Home	33	4	*12*	0	1	3	0	0	0	0	29	*88*	110	3.3	11	*10*	7	1	3	99	*90*
	Sanatorium	30	0	*0*	0	0	0	0	0	0	0	30	*100*	94	3.1	0	*0*	0	0	0	94	*100*
9	Home	33	3	*9*	2	0	1	0	0	0	0	30	*91*	90	2.7	6	*7*	4	1	1	84	*93*
	Sanatorium	30	0	*0*	0	0	0	0	0	0	0	30	*100*	83	2.8	0	*0*	0	0	0	83	*100*
12	Home	32 †	7	*22*	1	0	1	1	0	2	2	25	*78*	89	2.8	11	*12*	3	5	3	78	*88*
	Sanatorium	30	1	*3*	0	0	0	0	0	0	1	29	*97*	76	2 5	1	*1*	0	0	1	75	*99*

* For definition of complete test, see page 59.

** Even if the smear was positive (see page 73)

† Excluding one patient who deteriorated and had her chemotherapy changed (see page 79)

TABLE 22

RESULTS OF ISONIAZID-SENSITIVITY TESTS IN FEMALE PATIENTS TREATED WITH ISONIAZID PLUS PAS FOR A PERIOD OF 12 MONTHS *

Months after start of chemo-therapy	Treatment series	Total patients with cultures examined (a)	Culture-negative (no sensitivity test possible)	Culture-positive but no sensitivity result available	Patients culture-positive with sensitivity tests: total results available (b)	sensitive: no growth on 0.2 µg/ml	resistant: growth on 0.2 µg/ml, not on 1, repeated	resistant: growth on 1 µg/ml, not on 5	resistant: growth on 5 µg/ml, not on 50	resistant: growth on 50 µg/ml	total resistant to isoniazid: number	total resistant to isoniazid: % of (b)	total resistant to isoniazid: % of (a)
3	Home	33	19	0	14	13	0	1	0	0	1	*(7)* **	*3*
	Sanatorium	30	24	0	6	6	0	0	0	0	0	*(0)*	*0*
6	Home	33	29	0	4	1	1	1	1	0	3	*(75)*	*9*
	Sanatorium	30	30	0	0	0	0	0	0	0	0	—	*0*
9	Home	33	30	0	3	1	1	0	1	0	2	*(67)*	*6*
	Sanatorium	30	30	0	0	0	0	0	0	0	0	—	*0*
12	Home	32†	25	0	7	1	2	1	2	1	6	*(86)*	*19*
	Sanatorium	30	29	0	1	0	1	0	0	0	1	*(100)*	*3*

* All patients had strains sensitive to isoniazid and PAS before treatment.
** Percentages based on fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.
† Excluding one patient who deteriorated and had her chemotherapy changed.

TABLE 23

CLASSIFICATION OF DISEASE IN FEMALE PATIENTS AT THE END OF 12 MONTHS AS QUIESCENT, OF DOUBTFUL STATUS, RELAPSED OR ACTIVE ON THE BASIS OF CULTURE RESULTS DURING THE PERIOD

Bacteriological status at the end of 12 months	Home: number	Home: %	Sanatorium: number	Sanatorium: %
Patients bacteriologically quiescent : that is, patients whose cultures were all negative for at least the last three monthly examinations—i.e., at 10, 11 and 12 months				
First monthly examinations at which all the cultures were negative and remained so:				
1	4		7	
2	2		9	
3	9		6	
4	6		5	
5	0		0	
6	0		2	
7	0		0	
8	1		0	
9	0		0	
10	0		0	
Total patients with bacteriologically quiescent disease at 12 months	22	*67*	29	*94*
Patients bacteriologically of doubtful status : that is, patients whose cultures were all negative at three or more consecutive monthly examinations, but who produced an isolated positive culture at one of the last three monthly examinations—i.e., at 10, 11 or 12 months	3	*9*	0	*0*
Patients bacteriologically relapsed: that is, patients whose cultures were all negative at three or more consecutive monthly examinations, but who produced two or more positive cultures in the last three monthly examinations—i.e., at 10, 11 and 12 months	5	*15*	1	*3*
Patients bacteriologically active : that is, (*a*) patients whose cultures were never all negative at three consecutive monthly examinations	2	*6*	0	*0*
or (*b*) patients who deteriorated and had their chemotherapy changed	1	*3*	0	*0*
Total patients with bacteriologically relapsed or active disease at 12 months	8	*24*	1	*3*
Deaths	0	*0*	1	*3*
Total female patients	33	*100*	31	*100*

VII. THE INFLUENCE OF THE PRETREATMENT DIFFERENCES BETWEEN THE SERIES ON THE RESULTS OF TREATMENT

This section reports special analyses which were undertaken to investigate the influence of the pretreatment radiographic and bacteriological differences on the results of treatment in the two series. The procedure used was statistical standardization of the results of treatment to allow for the pretreatment differences.

PROCEDURE

Standardization was applied to various measures of progress in the two series to allow for the pretreatment differences between them. The principle underlying this technique is a comparison of the progress of patients in the home and sanatorium series with similar disease characteristics before treatment

The procedure was to subdivide the patients in each series into reasonably homogeneous subgroups, according to a pretreatment factor (or factors) which was known to be of prognostic importance, such as the extent of cavitation. A measure of response—for example, the proportion of patients bacteriologically negative on a single collection specimen at six months—was then derived for each subgroup. The comparison of this proportion for a subgroup of the home series with the proportion for the corresponding subgroup of the sanatorium series provided an indication of the relative progress under the two treatments of patients in a similar pretreatment condition. These comparisons for individual subgroups were combined into a single comprehensive comparison by averaging the proportions for each series separately, and comparing these averages.[1] A comparison undertaken in this way allow for differences between the series of patients being compared, in respect of the pretreatment factor (or factors) under study.

In the present study, measures of the radiographic and bacteriological response were standardized in this way for pretreatment differences in (1) the extent of cavitation, as assessed by Dr Ida B. Scudder ; (2) the number of lung zones involved in disease, as assessed by Dr Ida B. Scudder ; and (3) the extent of cavitation and the lung-zone involvement combined. It was decided to standardize for extent of cavitation and lung-zone involvement, both separately and together, because both were found to be of major prognostic importance in the present study (see page 87), as well as in previous investigations (Fox, Sutherland & Daniels, 1954 ; Tucker & Livings, 1955 ; Fox & Sutherland, 1956), and because the two series differed in both these respects at the start of treatment. Standardization for the bacterial content of the sputum before treatment, in addition, was not undertaken because there was evidence that it was of less prognostic importance and because the total number of patients was too small for acceptable standardization for three pretreatment differences simultaneously.

For the assessments of progress, four measures of radiographic response were used : (1) the percentage of patients showing considerable or exceptional improvement in the period 0-6 months ; (2) the same percentage for the period 0-12 months ; (3) the percentage of patients showing any grade of improvement in the period 6-12 months ; and (4) the percentage of patients who had had cavitation before treatment and in whom it had disappeared at 12 months. In addition, four measures of bacteriological response were used : (1) the percentage of patients with a negative culture on a single collection specimen at three months ; (2) the corresponding percentage at six months ; (3) the corresponding percentage at 12 months ; and (4) the percentage of patients no longer having bacteriologically active disease at the end of 12 months according to the definition adopted in this report (see page 77). The standardized percentages for all eight assessments were calculated for males and females separately, as well as for the two sexes combined.

[1] In calculating the averages, any subgroup represented in one series but not in the other was omitted, so as not to bias the comparison between the two series; in the comparisons made, no patients had to be omitted when standardizing for a single factor, but when standardizing for extent of cavitation and lung-zone involvement simultaneously, three home patients (two male, one female) were omitted when standardizing both sexes, three home patients when standardizing the males, and four home and four sanatorium patients when standardizing the females. The averages were weighted, the weights for corresponding subgroups in the two series being proportionate to the total numbers of patients in the corresponding subgroups combined; in other words, the technique was that of direct standardization, regarding the patients in the main analysis as the standard population.

RADIOGRAPHIC RESPONSE

The radiographic responses to treatment, standardized for pretreatment differences, are shown in Table 24. Considering first all patients, during the period 0-6 months the unstandardized percentages showing considerable or exceptional radiographic improvement were 30.0 of those at home and 38.0 of those in sanatorium, the former proportion being 79% of the latter. When allowance was made for the pretreatment differences in extent of cavitation between the series, the standardized percentages were 32.2 and 35.6 respectively ; that is, the contrast between the two series was substantially reduced, the response in the patients at home now being 90% of that of patients in sanatorium. Standardization for lung-zone involvement also slightly reduced the contrast between the series, the response in patients at home becoming 82% of that in sanatorium patients. When allowance was made for the two pretreatment differences simultaneously, the standardized percentages were 31.3 for patients at home and 35.3 for those in sanatorium (the former being 89% of the latter), compared with the unstandardized figures (already mentioned) of 30.0 and 38.0 respectively. Thus the differences between the radiographic progress of the home and sanatorium series during the first six months reflected in some measure, though not entirely, the pretreatment differences between the series in extent of cavitation and lung-zone involvement.

Considering the period 0-12 months, the percentages of patients showing considerable or exceptional radiographic improvement were 41.2 in the home series and 51.9 in the sanatorium series, the former being 79% of the latter. The contrast between these percentages was not reduced by standardization for extent of cavitation alone, but when both pretreatment factors were taken into account,

TABLE 24

PERCENTAGES OF PATIENTS SHOWING FAVOURABLE RADIOGRAPHIC RESPONSES, STANDARDIZED FOR PRETREATMENT DIFFERENCES IN EXTENT OF CAVITATION AND LUNG-ZONE INVOLVEMENT

Nature of radiographic response	Period	Standardization for pretreatment differences in :	Percentages for all patients			Percentages for males			Percentages for females		
			home	sana-torium	home as % of san.	home	sana-torium	home as % of san.	home	sana-torium	home as % of san.
Percentage of patients with considerable or exceptional radiographic improvement	0-6 months	(Unstandardized)	30.0	38.0	*79*	29.8	34.7	*86*	30.3	43.3	*70*
		Extent of cavitation	32.2	35.6	*90*	31.8	32.4	*98*	33.7	41.6	*81*
		Lung-zone involvement	30.8	37.6	*82*	32.6	34.0	*96*	28.7	43.5	*66*
		Cavitation *and* lung zones	31.3	35.3	*89*	33.9	32.1	*106*	32.1	30.4	*106*
	0-12 months	(Unstandardized)	41.2	51.9	*79*	40.4	51.0	*79*	42.4	53.3	*80*
		Extent of cavitation	41.9	53.1	*79*	40.4	50.5	*80*	46.2	48.8	*95*
		Lung-zone involvement	43.0	52.5	*82*	42.2	51.8	*81*	43.6	51.4	*85*
		Cavitation *and* lung zones	43.6	48.7	*90*	40.5	49.8	*81*	44.3	39.9	*111*
Percentage of patients with any degree of radiographic improvement	6-12 months	(Unstandardized)	23.8	39.2	*61*	23.4	38.8	*60*	24.2	40.0	*61*
		Extent of cavitation	22.1	39.6	*56*	21.6	39.5	*55*	22.4	42.7	*52*
		Lung-zone involvement	22.7	39.2	*58*	21.8	38.9	*56*	23.7	38.7	*61*
		Cavitation *and* lung zones	23.7	41.8	*57*	23.1	39.6	*58*	21.8	47.8	*46*
Percentage of patients with pretreatment cavitation in whom it disappeared	at 12 months	(Unstandardized)	36.6	54.2	*68*	36.6	50.0	*73*	36.7	60.7	*60*
		Extent of cavitation	41.9	49.4	*85*	41.4	47.0	*88*	41.9	52.5	*80*
		Lung-zone involvement	34.9	48.0	*73*	42.4	45.7	*93*	38.5	62.1	*62*
		Cavitation *and* lung zones	42.9	48.1	*89*	38.8	44.7	*87*	49.0	51.1	*96*

the standardized percentages were 43.6 for the home patients and 48.7 for those in sanatorium, the former being 90% of the latter.

In the second six months, on the other hand, the standardized percentages of patients showing any grade of radiographic improvement demonstrated a greater benefit to the sanatorium series than did the unstandardized percentages. Allowing for both pretreatment factors the standardized percentages were 23.7 for the home and 41.8 for the sanatorium series ; it will be recalled that practically all the radiographic changes in this period were minor (see page 69).

Lastly, standardization for both pretreatment factors considerably reduced the difference between the home and sanatorium series in respect of cavity closure in the 12-month period, the standardized percentages being 42.9 for the home and 48.1 for the sanatorium series, compared with the unstandardized percentages of 36.6 and 54.2.

It may be concluded that, after allowing for the pretreatment differences, the radiographic responses of the home and sanatorium patients of both sexes during the 12 months still showed a slight residual advantage to the sanatorium series ; in particular, minor radiographic improvements more frequently continued during the second six months in the sanatorium series.

Turning to the figures for males only, based on smaller totals of patients, the effect of standardization on the radiographic responses was similar to that for all patients. When allowance was made both for extent of cavitation and lung-zone involvement before treatment, the contrast between home and sanatorium males in the percentages showing considerable or exceptional improvement in the first six months was reversed in favour of the home males, although for the whole 12-month period it was practically unchanged. As regards radiographic improvement in the second six months, the contrast between the home and sanatorium series persisted, indicating that a greater proportion of sanatorium males showed continued minor radiographic improvements after the first six months; the standardized percentages (for both pretreatment factors) were 23.1 and 39.6. The contrast between the series in the percentage whose cavities had closed at 12 months was substantially reduced ; the standardized percentage for males at home was 38.8, and for males in sanatorium 44.7, compared with the unstandardized percentages of 36.6 and 50.0.

It may be concluded from all the above comparisons that after allowance had been made for the pretreatment differences, there was a residual advantage to the males in sanatorium, who had fared slightly better radiographically than those at home.

Considering the females, who were fewer in number than the males, standardization for both pretreatment differences simultaneously has reversed the position of the two series in terms of considerable and exceptional radiographic improvement during the period. Thus at six months the standardized percentage for the home females (32.1) was slightly *greater* than for the sanatorium females (30.4), the corresponding figures at 12 months being 44.3 and 39.9. Minor radiographic improvements in the second six months, after allowing for pretreatment differences, were commoner in the sanatorium than the home females. As regards cavity closure, the contrast between the two series almost disappeared on standardization for both factors, the standardized percentages being 49.0 for the home females and 51.1 for the sanatorium females, compared with unstandardized figures of 36.7 and 60.7 respectively.

In summary, there was little to choose between the radiographic progress of the females at home and that of the females in sanatorium, after allowance had been made for pretreatment radiographic differences.

A corresponding analysis (not tabulated) was undertaken, standardizing both for extent of cavitation and the bacterial content of the sputum (as graded on direct smear examination of a single collection specimen), and led to very similar conclusions.

BACTERIOLOGICAL RESPONSE

The bacteriological responses to treatment, standardized similarly for pretreatment differences in extent of cavitation, in lung-zone involvement, and in both factors, are shown in Table 25. Considering first all patients, the effect of allowing for the pretreatment differences in extent of cavitation and lung-zone involvement was a slight reduction in the contrast between the responses of home and sanatorium patients. This applies to all four responses —namely, the percentages of patients with negative cultures at three, six and 12 months, and the percentage no longer having bacteriologically active disease at 12 months. For example, the percentages

TABLE 25

PERCENTAGES OF PATIENTS SHOWING FAVOURABLE BACTERIOLOGICAL RESPONSES, STANDARDIZED FOR PRETREATMENT DIFFERENCES IN EXTENT OF CAVITATION AND LUNG-ZONE INVOLVEMENT

Nature of bacteriological response	Month	Standardization for pretreatment differences in :	Percentages for all patients			Percentages for males			Percentages for females		
			home	sana-torium	home as % of san.	home	sana-torium	home as % of san.	home	sana-torium	home as % of san.
Percentage of patients with negative culture on a single collection specimen	3	(Unstandardized)	67.5	78.9	*86*	63.8	74.5	*86*	72.7	86.2	*84*
		Extent of cavitation	68.8	75.9	*91*	65.6	72.0	*91*	73.3	82.6	*89*
		Lung-zone involvement	68.1	77.4	*88*	64.0	71.9	*89*	71.9	85.1	*84*
		Cavitation *and* lung zones	68.9	75.3	*92*	66.0	70.6	*93*	69.8	81.9	*85*
	6	(Unstandardized)	87.5	97.4	*90*	87.2	95.8	*91*	87.9	100.0	*88*
		Extent of cavitation	88.5	97.1	*91*	87.6	95.6	*92*	89.0	100.0	*89*
		Lung-zone involvement	88.7	97.2	*91*	88.6	95.8	*92*	88.8	100.0	*89*
		Cavitation *and* lung zones	90.5	97.3	*93*	91.7	95.1	*96*	86.4	100.0	*86*
	12	(Unstandardized)	87.0	93.5	*93*	88.6	89.6	*99*	84.8	100.0	*85*
		Extent of cavitation	89.2	92.3	*97*	89.5	88.5	*101*	89.1	100.0	*89*
		Lung-zone involvement	88.3	92.4	*96*	90.2	87.6	*103*	84.8	100.0	*85*
		Cavitation *and* lung zones	89.8	93.6	*96*	90.9	86.8	*105*	87.0	100.0	*87*
Percentage of patients no longer with active disease bacterio-logically	12	(Unstandardized)	83.8	92.4	*91*	89.4	89.8	*100*	75.8	96.7	*78*
		Extent of cavitation	85.6	92.1	*93*	90.4	88.9	*102*	77.7	97.6	*80*
		Lung-zone involvement	85.4	91.5	*93*	90.5	88.3	*102*	78.0	96.4	*81*
		Cavitation *and* lung zones	86.2	92.0	*94*	91.4	86.6	*106*	75.5	100.0	*76*

of all patients with negative cultures at six months, standardized for both extent of cavitation and lung-zone involvement, were 90.5 for home and 97.3 for sanatorium patients, compared with unstandardized percentages of 87.5 and 97.4 respectively. Considering the sexes separately, these effects are seen to stem from the males only. The less satisfactory bacteriological response in the home females, compared with the sanatorium females, persisted almost unaltered despite standardization ; in particular, taking both factors into account, the standardized percentages of patients no longer having active disease bacteriologically at 12 months were 75.5 for the females at home and 100.0 for those in sanatorium.

In summary, the bacteriological disadvantage to the males treated at home disappeared in part when allowance was made for pretreatment differences in extent of cavitation and lung-zone involvement, but the disadvantage to the females at home remained.

A corresponding analysis (not tabulated) was undertaken, standardizing both for extent of cavitation and the bacterial content of the sputum, and led to very similar conclusions.

It will be appreciated that standardization has been undertaken only for *some* of the important pretreatment differences. Thus, simultaneous standardization for the three main factors—namely, extent of cavitation, lung-zone involvement, and bacterial content of the sputum—as already explained, was not undertaken. Had it been practicable, it might have given a more complete indication of the residual differences in reponse between home and sanatorium patients. It must also be emphasized that, if pretreatment differences are large and the numbers of patients are small (as with the females in the present study), no standardization process is likely to be completely successful in taking account of all differences in response arising from the pretreatment differences.

VIII. PROGNOSTIC VALUE OF VARIOUS CLINICAL FEATURES BEFORE THE START OF TREATMENT

It is important to investigate which features of the disease at the start of treatment were associated with an unfavourable response to treatment. It was therefore decided to study the bacteriological status of the disease at 12 months in relation to various pretreatment factors—namely, the age (estimated), the ESR, the extent of cavitation and the total extent of the disease radiographically, and the bacterial content of the sputum. Since the findings have already been analysed in this report in detail for the males and females at home and in sanatorium, this section presents findings for all the patients of both sexes in both treatment series in the main analysis combined. The results are shown in Table 26.

ESTIMATED AGE

Of 54 patients estimated to be in the 12-24 age-group, six (11%) had bacteriologically active disease at 12 months, compared with eight (16%) of 50 in the 25-34 age group, two (7%) of 27 in the 35-44 age group, one (5%) of 20 in the 45-54 age group, and two (25%) of eight patients aged 55 or more. There was thus little apparent association between age and prognosis.

ERYTHROCYTE SEDIMENTATION RATE

Of 38 patients with an ESR of 101 or more before treatment, six (16%) had bacteriologically active disease at 12 months, compared with 11 (12%) of 93 with an ESR of 51-100 and one (4%) of 23 with an ESR of 21-50. There were only five patients with an ESR lower than 20 and one (20%) had active disease at 12 months. The findings suggest that patients with a high ESR were less likely to attain a satisfactory bacteriological status than those with lower ESRs.

CAVITATION

Of 59 patients with extensive cavitation 12 (20%) had bacteriologically active disease at 12 months, compared with five (9%) of 58 with moderate cavitation and two (5%) of 42 with little or no cavitation. Thus, the absence of cavitation and cavitation of limited extent were relatively good prognostic signs.

NUMBER OF LUNG ZONES INVOLVED IN DISEASE

Of 38 patients with six lung zones involved in disease, 11 (29%) had bacteriologically active disease at 12 months, compared with four (12%) of 34 with five zones, two (5%) of 44 with four zones, none (0%) of 22 with three zones, and two (10%) of 21 with two or one lung zones involved. Thus, the patients with widespread disease were less likely to fare well bacteriologically than those with disease of limited extent.

BACTERIAL CONTENT OF THE SPUTUM

The bacteriological status at 12 months was studied in relation to the bacterial content of the sputum on smear examination of a pretreatment collection specimen. Of 72 patients with a 3-plus smear, 10 (14%) had bacteriologically active disease at 12 months, compared with seven (15%) of 47 with a 2-plus smear, two (9%) of 22 with a 1-plus smear and none (0%) of 18 negative on smear. Thus there was a suggestion that 3-plus and 2-plus positive smears were associated with relatively unfavourable progress.

CLINICAL FEATURES BEFORE TREATMENT FOR THE PATIENTS WHO DIED

Since the measure of unfavourable progress which was used above was the bacteriological activity of disease at 12 months, the four patients who died do not appear in the figures. Of these deaths, one was non-tuberculous (due to electrocution at work), and so cannot be regarded as an adverse response to treatment.

For the three patients who died of tuberculosis, the estimated ages before the start of treatment were 20, 41 and 54 years, the ESRs were 90, 86 and 34, the cavitation was extensive for two patients and moderate for the third, the numbers of lung zones involved in disease were six for two and five for the third, and the bacterial contents of the sputum on direct smear were 3-plus, 2-plus and negative.

TABLE 26

BACTERIOLOGICAL STATUS AT 12 MONTHS ACCORDING TO CONDITION ON ADMISSION TO TREATMENT *

Condition on admission to treatment		Total survivors at 12 months	Bacteriological status at 12 months			
			quiescent	doubtful	active (or relapsed)	
					number	%
Age (estimated, in years)	12-24	54	42	6	6	*11*
	25-34	50	39	3	8	*16*
	35-44	27	25	0	2	*7*
	45-54	20	18	1	1	*(5)***
	55 or more	8	6	0	2	*(25)*
ESR (mm in 1 hr)	101 or more	38	29	3	6	*16*
	51-100	93	76	6	11	*12*
	21-50	23	22	0	1	*(4)*
	0-20	5	3	1	1	*(20)*
Extent of cavitation	Extensive	59	40	7	12	*20*
	Moderate	58	51	2	5	*9*
	Slight	26	24	1	1	*4*
	Nil	16	15	0	1	*(6)*
Number of lung zones involved in disease	6	38	26	1	11	*29*
	5	34	26	4	4	*12*
	4	44	40	2	2	*5*
	3	22	20	2	0	*(0)*
	2 or 1	21	18	1	2	*(10)*
Bacterial content of sputum (direct smear grade on collection specimen †)	3 - plus	72	55	7	10	*14*
	2 - plus	47	38	2	7	*15*
	1 - plus	22	20	0	2	*(9)*
	Negative	18	17	1	0	*(0)*
	Total patients	159	130	10	19	*12*

* Home and sanatorium series combined

** Percentages based on fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.

† For five home and four sanatorium patients, no collection specimen was available, but special estimates of bacterial content were made from results of spot specimens (see page 64).

IX. FURTHER BACTERIOLOGICAL FINDINGS

This section contains a number of subsidiary bacteriological findings for patients in the main analysis, for which it is not important to distinguish between male and female patients. The findings are therefore presented for both sexes together.

SMEAR-POSITIVE CULTURE-NEGATIVE RESULTS

As indicated when the main bacteriological findings were presented (see page 73), a number of smear-positive culture-negative results were obtained, particularly in the first six months of treatment, and these were all included with the smear-negative culture-negative results, on the strength of findings which are reported below.

The frequency with which such results occurred during the 12-month period is shown in Table 27, which combines the findings for home and sanatorium patients. It will be seen from the right-hand section of the table that before the start of treatment, smear-positive culture-negative results represented only 1.2% of the 569 positive results (1.0% in the home series and 1.5% in the sanatorium series). After the start of treatment, the frequency increased to a maximum at five months, when such results occurred in 13 (28.9%) of 45 positive specimens—namely, in five of 26 specimens from home patients and in eight of 19 from sanatorium patients. In the later months, the frequency of smear-positive culture-negative results decreased, although such results were obtained occasionally throughout the rest of the 12 months. From the last column of the left-hand section of the table, referring to the patients tested, it will be seen that, although the smear-positive culture-negative results made a trivial contribution to the number of patients who were positive on smear before the start of treatment, the contribution, particularly in the middle months of the treatment, was of considerable importance. Thus, at five months 11 (37.9%) of 29 patients (four of 15 at home and seven of 14 in sanatorium) yielded one or more smear-positive culture-negative results, any other available results for the month being smear- and culture-negative. If these results are accepted as positive bacteriological findings, then at five months 29 patients (15 at home and 14 in sanatorium) were bacteriologically positive. If, on the other hand, these results are regarded as equivalent to negative bacteriological findings, then the number of patients at five months who were bacteriologically positive falls to 18 (11 at home and seven in sanatorium)—a substantial difference.

Other analyses were therefore undertaken to investigate the interpretation of these smear-positive culture-negative results, which, in all, were reported in 27 of the home and 24 of the sanatorium patients. Such a result occurred on a single occasion in 19 home and 15 sanatorium patients. It occurred more than three times in only three patients—namely, one at home (four times) and two in sanatorium (four times and seven times, respectively). In two home and four sanatorium patients there was an interval of more than three months between the first and last occasions on which a smear-positive culture-negative result was obtained—namely, five and seven months respectively for the home patients and four, five, six and six months respectively for the sanatorium patients. The grading of positivity of the smear was 1-plus in 36 (88%) of the total of 41 tests in the home series and in 37 (86%) of 43 tests in the sanatorium series. Four (15%) of the 27 home and two (8%) of the 24 sanatorium patients who had one or more smear-positive culture-negative results had bacteriologically active disease at the end of 12 months, compared with nine (17%) of the 53 home and four (7%) of the 55 sanatorium patients who had no such results at any time; there was thus no association between the occurrence of these results and bacteriological status at 12 months. Finally, it is possible that smear-positive culture-negative specimens might represent isoniazid-resistant bacilli which had failed to grow on culture because of supposedly special growth requirements. Further examination of the data, however, has shown that specimens obtained after the development of isoniazid resistance showed no higher an incidence of smear-positive culture-negative results than did specimens from patients who did not develop isoniazid resistance.

In summary, the occurrence of smear-positive culture-negative results before the start of treatment was rare. Such results increased to a maximal frequency in the middle months of treatment, and subsequently decreased. Further, the result was an isolated observation in the majority of patients in whom it occurred, and it was very uncommon for it to occur frequently, or over a long period of time.

TABLE 27

SMEAR-POSITIVE CULTURE-NEGATIVE RESULTS DURING THE 12-MONTH PERIOD *

Months after start of chemotherapy	Patients tested					Specimens examined		
	total patients with results of at least one complete test available **	total patients positive either on smear or on culture (a)	number of patients with smear-positive culture-negative results	patients, all of whose positive results were smear-positive culture-negative		total specimens positive either on smear or on culture (b)	smear-positive culture-negative results	
				number	% of (a)		number	% of (b)
0	160	159	7	1	*0.6*	569	7	*1.2*
1	158	132	6	2	*1.5*	287	8	*2.8*
2	159	103	12	5	*4.9*	207	12	*5.8*
3	160	68	13	8	*11.8*	112	15	*13.4*
4	160	26	9	6	*23.1*	42	9	*21.4*
5	159	29	12	11	*37.9*	45	13	*28.9*
6	160	19	4	4	*(21.1)* †	36	6	*16.7*
7	159	20	3	3	*(15.0)*	35	3	*8.6*
8	158	20	3	3	*(15.0)*	37	3	*8.1*
9	159	16	3	3	*(18.8)*	30	3	*10.0*
10	158	15	1	1	*(6.7)*	30	1	*3.3*
11	157	18	1	1	*(5.6)*	32	1	*3.1*
12	157	20	2	1	*(5.0)*	38	3	*7.9*

* Home and sanatorium series combined ** For definition of complete test, see page 59.
† Percentages based on fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.

Most of the smears from these specimens were graded as only 1-plus. There was no association with bacteriological activity at 12 months or with the presence of isoniazid-resistant strains. On the basis of these findings, it has been considered justifiable to conclude that the bacilli in these specimens were non-viable, and to regard all these results as bacteriologically negative findings.

PATTERN OF ISONIAZID RESISTANCE DURING TREATMENT

The pattern of isoniazid resistance has been studied for the 27 patients in the two series combined, who yielded one or more isoniazid-resistant cultures in the course of the 12 months. It will be recalled that one sensitivity test was performed for each patient

monthly, if a positive culture was obtained. In eight patients (five male, three female), once isoniazid resistance had developed, there was at least one monthly positive culture up to and including 12 months, and these were consistently resistant (apart from one isolated sensitive result among six resistant results in one patient, and one among nine in another). In these eight patients the number of resistant cultures obtained from each patient ranged from six to ten. In eight more patients (four male, four female), resistance to isoniazid, once it had emerged, was a consistent finding at all subsequent positive tests, but some of the subsequent cultures were negative (in one patient following a change of chemotherapy). In this group of patients the number of resistant cultures obtained from each patient ranged from three to eight. There were a further two patients who had one and two resistant cultures respectively, followed by a period of culture negativity, but in whom a single sensitive culture was obtained subsequently, at nine months and at 12 months respectively. There were also two patients who had resistant cultures at 12, and at 11 and 12 months, respectively, for whom it is not possible to say whether these were isolated occurrences or the commencement of persisting positivity with isoniazid resistance. Finally, there were seven patients who yielded an isolated resistant result amidst a series of negative cultures.

It therefore seems likely that of these 27 patients, 16 (of whom nine were male and seven female) may have been a source of danger to the public health during the course of the 12 months, and perhaps subsequently as well. These were the eight patients who were consistently positive bacteriologically with persistently isoniazid-resistant organisms, and the eight (including the patient who had his chemotherapy changed) whose cultures were intermittently positive, but consistently isoniazid-resistant. These 16 patients represent 9.8% of the 163 in the main analysis. The catalase activity of the resistant strains from these patients is referred to later (see page 93).

RELATIONSHIP OF BACTERIOLOGICAL STATUS AT THE END OF 12 MONTHS TO EMERGENCE OF ISONIAZID RESISTANCE DURING TREATMENT

An analysis was undertaken to relate the bacteriological status at the end of 12 months to the emergence of one or more isoniazid-resistant cultures during treatment. Of the 130 patients in the two series combined who attained bacteriological quiescence at the end of 12 months, 126 (97%) had yielded only isoniazid-sensitive results and four had yielded isolated resistant results. Of the 10 patients whose disease was of doubtful status at 12 months, three had yielded only sensitive results and the other seven resistant results, this being an isolated occurrence in five. Of the 19 patients whose disease was active or relapsed, three (16%) had yielded only sensitive results and 16 had yielded resistant results, the number of resistant cultures ranging from two to 10 ; that is, none had yielded an isolated resistant result. It may be concluded that there was an association between isoniazid-sensitive results during the course of treatment and bacteriological quiescence at 12 months. Resistant results during the course of the 12 months were commonly associated with active disease bacteriologically at 12 months and, to a lesser extent, with disease of doubtful status.

REAPPEARANCE OF ISONIAZID-SENSITIVE CULTURES FOLLOWING BACTERIOLOGICAL NEGATIVITY

Of a total of 18 positive cultures with sensitivity results at 12 months, five were isoniazid-sensitive. Three of these were from patients who had yielded only sensitive results for all the cultures obtained during the 12 months. These three patients had had periods of bacteriological negativity of four, six and nine months respectively, before the re-emergence of isoniazid-sensitive strains. The isoniazid-sensitive strain was an isolated occurrence at 12 months in two patients and occurred both at 11 and at 12 months in the third. In other words, no patient in the main analysis remained consistently bacteriologically positive with isoniazid-sensitive organisms throughout the 12 months.

CATALASE ACTIVITY

Qualitative tests of catalase activity were carried out on 535 sensitive cultures obtained before and during treatment, and on 112 of the 115 resistant cultures that were obtained during treatment. A sample of the growth on the drug-free slope and on each of the drug-containing slopes in the isoniazid-sensitivity test was taken on a nickel-chrome wire loop and immersed in an aqueous solution of 1.5% (w/v) hydrogen peroxide and 5% Tween 80. The liberation of bubbles of gas was observed and graded as follows. The usual degree of activity found with isoniazid-sensitive strains of tubercle bacilli was graded as ++ ; a grading of +++

TABLE 28

CATALASE ACTIVITY OF THE GROWTH ON DRUG-FREE SLOPES IN MONTHY SENSITIVITY TESTS ON ISONIAZID-RESISTANT CULTURES *

Months after start of chemotherapy	Total results	Qualitative test				Semiquantitative test			
		grade				% activity			
		+++	++	+	0	*100-70*	*60-20*	*10-0*	average
0	—	—	—	—	—	—	—	—	—
1	—	—	—	—	—	—	—	—	—
2	—	—	—	—	—	—	—	—	—
3	2	0	2	0	0	2	0	0	*90*
4	4	1	2	0	1	3	0	1	*68*
5	8	0	4	1	3	3	1	4	*38*
6	9	0	3	4	2	3	3	3	*47*
7	12	0	5	4	3	3	3	6	*35*
8	15	0	8	3	4	4	5	6	*37*
9	10	0	7	1	2	5	3	2	*53*
10	12	0	8	2	2	4	4	4	*42*
11	14	0	9	5	0	7	6	1	*59*
12	13	0	6	4	3	6	3	4	*44*
Total	99	1	54	24	20	40	28	31	*46*

* Home and sanatorium series combined

represented a greater activity, and + represented a lesser activity ; no activity was graded as 0. A semiquantitative method (Kreis, Le Joubioux & Pariente, 1956; Kreis & Le Joubioux, 1957) was also carried out on 22 sensitive cultures (10 before treatment and 12 during treatment) and on 99 resistant cultures obtained during treatment. In this method, a suspension of the organisms was held in contact with a 0.3% (w/v) solution of hydrogen peroxide for one hour at 8°C; the residual peroxide was then titrated with acid permanganate, and the result was expressed as the percentage of the original concentration of peroxide which was no longer present (to the nearest 10%). These tests were not carried out on all cultures as they were introduced only after the study was already under way.

The results of qualitative catalase tests on 259 sensitive pretreatment cultures showed that 2 (0.8%) had +++ activity, 249 (96.1%) ++ activity and 8 (3.1%) + activity ; none of the pretreatment cultures had 0 activity. The semiquantitative tests on 22 sensitive cultures gave an average result of 88% activity, with a range from 70% to 100%. After the start of treatment, qualitative catalase tests were performed on 276 isoniazid-sensitive strains ; 8 (2.9%) gave +++ results, 263 (95.3%) ++ results, 3 (1.1%) + results and 2 (0.7%) negative results. Of the two cultures with no catalase activity, one was obtained at the second month and was preceded and succeeded by sensitive strains with ++ activity ; the second was obtained at the twelfth month, and all preceding cultures had been sensitive with ++ catalase activity. Thus, apart from the cultures with no catalase activity, the distributions of the qualitative tests were similar for pretreatment and post-treatment sensitive strains.

The results of qualitative and semiquantitative tests, carried out on the growth from the drug-free slope in the isoniazid-sensitivity test for the 99 resistant cultures for which both results are available, are shown in Table 28. Compared with sensitive cultures, the degree of catalase activity of isoniazid-resistant strains was reduced. Thus, 44% of the 99 cultures yielded + or 0 activity, compared with 3% of 259 pretreatment and 2% of 276 post-treatment sensitive strains. However, it is noteworthy that 56% of 99 resistant strains, as estimated by the qualitative test, and 40%, as estimated by the semiquantitative test, still retained as high a degree of catalase activity as the sensitive strains—that is, ++ or +++ in the qualitative and 70% to 100% in the semiquantitative test. There was some slight evidence that the catalase activity of cultures tested at three and four months was greater than for those tested in subsequent months. Thus, one of six strains tested at three and four months by the qualitative method had reduced activity (+ or 0), whereas from five to 12 months, 43 (46%) of 93 strains had reduced activity. Correspondingly, the averages for the semiquantitative tests were lower from five to 12 months than those at three and four months.

For resistant strains, qualitative catalase tests were performed on the growth from the isoniazid-containing slopes of the isoniazid-sensitivity tests as well as on the drug-free slopes. The results are shown in Table 29. The distributions of catalase activity of growths from the slopes containing 0 and 0.2 μg/ml isoniazid were very similar; 63 (56%) of 112 tests from drug-free slopes yielded ++ or +++ results and 56 (55%) of 102 tests from 0.2 μg/ml isoniazid slopes yielded the same degree of activity. The growths on higher concentrations of isoniazid, however, showed a progressive decline in catalase activity ; the percentages with ++ or +++ activity were 29% of 69 tests from 1 μg/ml slopes, 24% of 34 tests from 5 μg/ml slopes and 0% of 17 tests from 50 μg/ml slopes. A further analysis, not tabulated, showed a possible tendency for the catalase activity of the growth from isoniazid-containing slopes to decrease between three and five months, but no tendency for the activity to alter during the rest of the 12 months.

TABLE 29

RESULTS OF QUALITATIVE TESTS OF CATALASE ACTIVITY OF THE GROWTHS IN SENSITIVITY TESTS ON ISONIAZID-RESISTANT CULTURES, ACCORDING TO THE ISONIAZID CONTENT OF THE SLOPE *

Isoniazid content of slope in μg/ml	Qualitative test				
	total results	grade			
		+++	++	+	0
0	112	1	62	25	24
0.2	102	0	56	22	24
1	69	0	20	20	29
5	34	0	8	9	17
50	17	0	0	3	14

* Home and sanatorium series combined

Reference was made earlier (see page 91) to 16 patients who, because they yielded positive and isoniazid-resistant bacteriological findings repeatedly, were considered to be a possible source of danger to the public health. The catalase activity of the resistant strains from these patients is of special interest since reduced or absent catalase activity is often associated with a reduction in the virulence of the strain in the guinea-pig, an observation which some authorities consider also applies to man (Middlebrook & Dressler, 1954 ; Schweiger & Vandra, 1958). The results of the tests of catalase

TABLE 30

RESULTS OF PAS-SENSITIVITY TESTS IN PATIENTS TREATED WITH ISONIAZID PLUS PAS FOR A PERIOD OF 12 MONTHS *

Months after start of chemotherapy	Treatment series	Total patients with cultures examined (a)	Culture-negative (no sensitivity test possible)	Culture-positive but no sensitivity result available	Patients culture-positive with sensitivity tests							
					total results available (b)	sensitive	resistant			total resistant to PAS		
						resistance ratio of 2 or less	resistance ratio of 4, repeated	resistance ratio of 8	resistance ratio of 16 or more	number	% of (b)	% of (a)
1	Home	81	12	4	65	61	1	3	0	4	*6*	*5*
	Sanatorium	78	16	3	59	57	1	1	0	2	*3*	*3*
2	Home	81	27	1	53	47	2	2	2	6	*11*	*7*
	Sanatorium	78	34	3	41	39	0	2	0	2	*5*	*3*
3	Home	81	45	1	35	31	0	3	1	4	*11*	*5*
	Sanatorium	79	54	1	24	23	0	1	0	1	*(4)***	*1*
4	Home	81	68	0	13	12	0	0	1	1	*(8)*	*1*
	Sanatorium	79	72	0	7	6	1	0	0	1	*(14)*	*1*
5	Home	80	69	1	10	7	1	1	1	3	*(30)*	*4*
	Sanatorium	79	72	0	7	6	0	1	0	1	*(14)*	*1*
6	Home	81	70	0	11	9	0	2	0	2	*(18)*	*2*
	Sanatorium	79	75	0	4	3	0	0	1	1	*(25)*	*1*
7	Home	80	68	0	12	10	0	1	1	2	*(17)*	*3*
	Sanatorium	79	74	1	4	2	0	1	1	2	*(50)*	*3*
8	Home	79	66	0	13	8	0	0	5	5	*(38)*	*6*
	Sanatorium	79	75	1	3	2	0	1	0	1	*(33)*	*1*
9	Home	80	71	1	8	4	0	2	2	4	*(50)*	*5*
	Sanatorium	79	75	4	4	2	0	0	2	2	*(50)*	*3*
10	Home	79†	71	0	8	2	0	0	6	6	*(75)*	*8*
	Sanatorium	79	73	0	6	5	0	0	1	1	*(17)*	*1*
11	Home	79†	65	1	13	8	0	0	5	5	*(38)*	*6*
	Sanatorium	78	76	0	2	1	0	0	1	1	*(50)*	*1*
12	Home	78††	65	0	13	6	2	1	4	7	*(54)*	*9*
	Sanatorium	79	73	2	4	2	0	2	0	2	*(50)*	*3*

* Both sexes, home and sanatorium series combined; all patients had strains sensitive to isoniazid and PAS before treatment.

** Percentages based on fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.

† Excluding one home patient who deteriorated and had his chemotherapy changed after nine months

†† Excluding two home patients who deteriorated and had their chemotherapy changed after nine and 11 months respectively

activity of the growth on the drug-free slope in the sensitivity test for the last strain obtained from each of these patients showed that nine had normal (++) activity, five had reduced (+) activity, and two had no activity. The corresponding figures for the growths on the 0.2 μg/ml isoniazid slope were nine with ++ activity, six with + activity and one with no activity. Closely similar distributions of catalase activity were obtained for the two preceding resistant strains from each patient. It may be concluded that a proportion of the strains had reduced or no catalase activity, and that this applied to the resistant component of these strains.

PAS SENSITIVITY

Table 30 sets out the results of the PAS-sensitivity tests for the patients in the main analysis. At three months the majority of results were still sensitive; only four of the 35 strains from 81 home patients and one of the 24 strains from 79 sanatorium patients were resistant. By six months, two of the 11 strains tested in the home series and one of the four strains in the sanatorium series were resistant. There was a tendency for a larger proportion of the strains to be resistant in the later months of treatment, and at nine months, four of eight strains in the home series and two of four in the sanatorium series were resistant. The corresponding figures at 12 months were seven of 13 in the home series and two of four in sanatorium. Of the six home patients who yielded sensitive strains at 12 months, four had yielded only sensitive strains throughout the course of treatment. The corresponding figure for the sanatorium group was one of two patients.

In summary, the proportion of positive strains which was PAS-resistant at any month was similar in the two series, and only twice exceeded 50%. In terms of absolute numbers, the home series yielded more positive cultures and, thus, more resistant strains.

RELATIONSHIP BETWEEN EMERGENCE OF ISONIAZID AND PAS RESISTANCE DURING TREATMENT

Resistance to isoniazid was observed in 27 (16.6%), and to PAS in 29 (17.8%) of the total of 163 patients in the main analysis. Table 31 sets out the data on the relationship between the emergence of resistance to isoniazid and to PAS. It will be seen, first, that for 121 patients all the tests were sensitive to both drugs. There were five instances of resistance to isoniazid with sensitivity to PAS on the same strain, with previous results all sensitive, but with no subsequent tests. These were all obtained at 10, 11 or 12 months. Conversely, there were six examples of resistance to PAS with sensitivity to isoniazid on the same strain, with previous results all sensitive, but with no subsequent tests. Of these, five occurred at one to three months, and one at 12 months. Thus, with isolated resistant results, PAS resistance occurred early and isoniazid resistance occurred late.

The emergence of resistance to isoniazid, with persisting sensitivity to PAS in tests at subsequent months, was observed in seven patients. The last occasion on which it was known that the strain was still sensitive to PAS ranged from two to nine months after the emergence of isoniazid resistance. In four of these patients sensitivity to PAS was found in at least three isoniazid-resistant cultures obtained during the second six months of treatment. Conversely, there were eight instances of the emergence of resistance to PAS with continuing sensitivity to isoniazid, the last isoniazid-sensitivity test being one month later in six patients and three and seven months later respectively in the remaining two. Thus, cultures remained positive, and sensitive to the companion drug, for a longer period after the emergence of isoniazid resistance than after the emergence of PAS resistance. This suggests that a finding of isoniazid resistance is associated with a greater tendency to persisting subsequent positivity than a finding of PAS resistance.

Of a total of 16 patients who developed resistance to isoniazid and later produced positive cultures, nine subsequently developed resistance to PAS, from one to six months later. Conversely, of the total of 12 patients who developed resistance to PAS and later produced positive cultures, four subsequently developed resistance to isoniazid, from two to 10 months later. Thus, the development of PAS resistance was less likely to be followed by resistance to isoniazid than the development of isoniazid resistance by resistance to PAS. There were only two examples of the simultaneous emergence of resistance to both drugs ; these occurred in the second and the eighth month respectively.

The time of emergence of resistance to each drug was investigated. Of the 27 patients with isoniazid-resistant strains, resistance first appeared within six months of starting treatment in 14 (52%). In only one (4%) of these did it appear within two months. In contrast, in the 29 patients with PAS-

TABLE 31

THE RELATIONSHIP OF THE EMERGENCE OF ISONIAZID- AND PAS-RESISTANT STRAINS DURING TREATMENT *

	Number of patients		
		Month isoniazid resistance emerged	PAS sensitivity subsequently
Resistant to isoniazid when still sensitive to PAS (21 patients)	5	10, 10, 11, 11, 12	No subsequent positive culture
	7	3, 5, 5, 6, 7, 7, 8	Sensitive subsequently—*respective* month of last PAS-sensitive test 12, 10, 12, 11, 9, 10, 12
	9	3, 3, 4, 4, 5, 5, 5, 6, 7	Resistant subsequently—*respective* month of first PAS-resistant test 4, 5, 6, 10, 6, 9, 10, 7, 12
		Month PAS resistance emerged	Isoniazid sensitivity subsequently
Resistant to PAS when still sensitive to isoniazid (18 patients)	6	1, 1, 1, 3, 3, 12	No subsequent positive culture
	8	1, 1, 2, 2, 2, 2, 3, 5	Sensitive subsequently—*respective* month of last isoniazid-sensitive test 2, 4, 3, 3, 3, 3, 4, 12
	4	1, 2, 2, 4	Resistant subsequently—*respective* month of first isoniazid-resistant test 11, 4, 7, 8
		Month both isoniazid and PAS resistance emerged	
Simultaneous emergence of resistance to isoniazid and PAS	2	2, 8	—
All available tests sensitive to isoniazid and PAS	121	—	—
No information available	1	—	—

* Home and sanatorium series combined

resistant strains, resistance first appeared in 22 (76%) within the first six months and in 13 (45%) within the first two months. Thus, PAS resistance tended to emerge earlier than isoniazid resistance. Moreover, altogether 120 sensitivity results were obtained for the 27 patients with isoniazid-resistant strains from the month of the first emergence of isoniazid resistance to the end of the 12 months. Of these, 115 were isoniazid-resistant and only five were isoniazid-sensitive. On the other hand, 78 sensitivity results to PAS were obtained from the 29 patients with PAS-resistant strains during the course of the 12 months, from the time of the first emergence of PAS resistance. Of these, 57 were PAS-resistant and 21 were PAS-sensitive. Thus, when resistance emerged, the isoniazid-sensitivity results were highly consistent, whereas the PAS-sensitivity results were more variable.

RELATIONSHIP OF EMERGENCE OF ISONIAZID RESISTANCE TO PRETREATMENT PAS-SENSITIVITY RESULTS

There is evidence (Great Britain, Medical Research Council, 1955) that if patients have pretreatment strains resistant to PAS they are not protected against the risk of the emergence of isoniazid-resistant organisms when treated with isoniazid plus PAS. If the definitions of PAS resistance used in the present report for the pretreatment strains have been set too high, then some of the patients classified as having PAS-sensitive organisms before treatment may really have had PAS-resistant organisms before treatment. Such an occurrence might underlie the failure of the combination of isoniazid and PAS used in this study to prevent the emergence of isoniazid resistance in some patients. An analysis was

therefore undertaken of the emergence of isoniazid resistance during treatment, in relation to the findings of the pretreatment PAS-sensitivity tests. For this purpose the 158 patients in the main analysis who survived to the end of the 12 months were studied, together with four of the six patients who had PAS-resistant organisms before treatment according to the definition used in the present report (see page 60) (these were the four patients who received uninterrupted chemotherapy with isoniazid plus PAS for the 12 months). The great majority—namely, 153 (94.4%) of the total of 162 patients—had PAS-sensitivity tests performed on two specimens of sputum before treatment, and if there was any doubt in the interpretation of either result the test was repeated. Thus, when a patient was classified as having PAS-sensitive organisms before treatment, this was, in the great majority of cases, on the basis of two clearly sensitive results on separate strains. If one of the two strains gave a doubtful result—that is, a resistance ratio of four—a second sensitivity test was undertaken on the strain, giving three pretreatment results for the patient. If both strains gave a resistance ratio of four, both tests were repeated, making in all, four pretreatment sensitivity results. The results of these tests have been used to classify the patients into four subgroups, one termed " resistant ", two termed " doubtfully resistant ", and one termed " sensitive ". The " resistant " subgroup contains the four patients whose strains conformed to the pretreatment definition of PAS resistance. The " doubtfully resistant A " subgroup consists of 14 patients in whom either both strains yielded resistance ratios of four, followed by resistance ratios of two or less on retest, or one strain yielded a resistance ratio of eight followed by a resistance ratio of two or less, the other being clearly sensitive. The " doubtfully resistant B " subgroup contains 25 patients who yielded a single resistance ratio of four followed by a resistance ratio of two or less on the same strain, the result of the test on the other strain also being two or less. The 119 patients in the " sensitive " subgroup yielded only resistance ratios of two or less.

The results of isoniazid-sensitivity tests in the course of treatment are summarized for each of these four subgroups in Table 32 for home and sanatorium patients combined. The percentage of isoniazid-resistant strains was very similar in all four subgroups. Thus, one of the four patients in the " resistant " subgroup before treatment yielded isoniazid-resistant results during treatment. Two (14%) of the 14

TABLE 32
EMERGENCE OF ISONIAZID RESISTANCE DURING TREATMENT RELATED TO THE RESULTS OF THE PRETREATMENT PAS-SENSITIVITY TESTS *

Pretreatment PAS sensitivity **	Total †	Isoniazid-sensitivity test results during treatment			
		all sensitive		one or more resistant	
		number	%	number	%
Resistant	4	3	(75) ††	1	(25)
Doubtfully resistant A	14	12	(86)	2	(14)
Doubtfully resistant B	25	21	84	4	16
Sensitive	119	98	82	21	18

* Home and sanatorium series combined

** Definitions : Resistant — Resistant before treatment according to definition on page 60, and not included in the main analysis

Doubtfully resistant A — Resistance ratio of 4 occurring twice, or resistance ratio of 8 followed by resistance ratio of 2 or less, either on the same or on a second strain

Doubtfully resistant B — Resistance ratio of 4 occurring once only, all other test results being 2 or less

Sensitive — Only resistance ratios of 2 or less

† Excluding four patients in the main analysis who died (three were in the Sensitive and one—electrocuted whilst at work—was in the Doubtfully resistant A category), and one patient with no pretreatment sensitivity tests

†† Percentages based upon fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.

patients in the " doubtfully resistant A " subgroup yielded at least one isoniazid-resistant result during treatment; the corresponding proportions for the " doubtfully resistant B " and " sensitive " subgroups were 16% of 25 and 18% of 119 patients.

It may be concluded that the emergence of isoniazid resistance was not related to the level of PAS sensitivity before treatment. There is thus no evidence that the misclassification as sensitive of strains from patients with genuinely PAS-resistant strains before treatment could account for the emergence of isoniazid resistance during the course of treatment in this study.

The findings of this and the preceding subsection indicate that PAS-sensitivity tests, as carried out and interpreted in this study, are less useful than isoniazid-sensitivity tests. They are not as consistent, and are also less indicative either of a poor subsequent bacteriological response or of the likelihood of resistance to the companion drug emerging. On the other hand, the results presented in Table 30 show that in the later months of treatment the proportion of PAS-resistant strains increased. This suggests that the test has at least some value. Finally, there is preliminary evidence (to be reported elsewhere) that Indian strains of tubercle bacilli differ from British strains in their behaviour in PAS-sensitivity tests, and that the definitions of resistance employed in this report, which are appropriate for British strains, may be less appropriate for those of Indian origin.

RELATIONSHIP OF BACTERIOLOGICAL STATUS AT THE END OF 12 MONTHS TO PRETREATMENT PAS-SENSITIVITY RESULTS

A further analysis was undertaken to investigate whether any patients with PAS-resistant organisms before treatment had been misclassified as having PAS-sensitive organisms. Such an occurrence might account for the presence of bacteriological activity at the end of 12 months. The patients were therefore classified into the same four subgroups as in the previous subsection, according to the results of the pretreatment PAS-sensitivity tests. The bacteriological status at the end of 12 months for each of the subgroups is shown in Table 33, for home and sanatorium patients combined. Three of four patients with resistant results before treatment were bacteriologically quiescent at 12 months compared with 86% of 14 in the " doubtfully resistant A " subgroup, 84% of 25 in the " doubtfully resistant B "

TABLE 33

BACTERIOLOGICAL STATUS OF PATIENTS AT THE END OF 12 MONTHS RELATED TO THE RESULTS OF THE PRETREATMENT PAS-SENSITIVITY TESTS *

Pretreatment PAS sensitivity **	Total patients †	Bacteriological status at end of 12 months					
		quiescent		doubtful status		active or relapsed	
		number	%	number	%	number	%
Resistant	4	3	(75)††	0	(0)	1	(25)
Doubtfully resistant A	14	12	(86)	1	(7)	1	(7)
Doubtfully resistant B	25	21	84	1	4	3	12
Sensitive	119	96	81	8	7	15	13

* Home and sanatorium series combined

** Definitions : Resistant — Resistant pretreatment according to definition on page 60, and not included in the main analysis

Doubtfully resistant A — Resistance ratio of 4 occurring twice, or resistance ratio of 8 followed by resistance ratio of 2 or less, either on the same or on a second strain

Doubtfully resistant B — Resistance ratio of 4 occurring once only, all other test results being 2 or less

Sensitive — Only resistance ratios of 2 or less

† Excluding four patients in the main analysis who died (three were in the Sensitive and one—electrocuted whilst at work—was in the Doubtfully resistant A category), and one patient with no pretreatment sensitivity tests

†† Percentages based upon fewer than 25 observations are enclosed in parentheses, as an indication of the small totals.

subgroup and 81% of 119 patients in the " sensitive " subgroup. It may be concluded that the bacteriological status at the end of 12 months was not related to the level of pretreatment PAS sensitivity. There is thus no suggestion that unfavourable bacteriological results of treatment in this study are referable to " cryptic " PAS resistance before treatment (Crofton, 1957).

STREPTOMYCIN SENSITIVITY

Streptomycin was not included in the standard chemotherapy and streptomycin-sensitivity tests were therefore not undertaken during treatment. Tests were, however, performed on the pretreatment cultures for 183 patients. The great majority of patients had two sensitivity tests and a small number only one. Five patients yielded streptomycin-resistant strains. Interrogation on several occasions and further inquiries revealed that only one of these had had previous chemotherapy likely to have been antituberculous; he also had an isoniazid-resistant strain. It is therefore probable that four (2.2%) of the 183 patients had been infected with streptomycin-resistant strains—that is, had primary streptomycin resistance. These patients were retained in the main analysis since the standard chemotherapy did not contain streptomycin.

X. TOXICITY AND OTHER COMPLICATIONS

This section reviews the toxic manifestations, certain other incidental complications of treatment and hospital admissions in the whole group of 193 patients originally allocated to treatment. It is not restricted to the patients in the main analysis.

TOXICITY

Gastro-intestinal side effects were completely unimportant in both series; it was not necessary to reduce the dosage of the medicament for any patient on account of them. One home patient had severe diarrhoea and oedema on admission to treatment and, because it was uncertain whether the condition was aggravated by the PAS, this medicament was replaced by streptomycin for three weeks; PAS was then resumed without a recurrence of the symptoms. Very occasionally patients complained of a burning sensation after taking an individual dose of medicine on an empty stomach.

Five patients (four home, one sanatorium) developed jaundice, all within the first ten weeks of treatment. One (home) then took indigenous medicine, discharged himself, and the cause of the jaundice is uncertain. Three others (two home, one sanatorium), one of whom also had a rash, rapidly resumed full dosage of the drug, and it was considered likely that two, if not all three, had had infective hepatitis. The fifth patient (home) had oedema of the face and hands, conjunctivitis and jaundice. The two former conditions recurred during three attempts at desensitization to PAS, and the treatment was changed on the grounds of PAS toxicity.

Four other patients (one home, three sanatorium) developed rashes in the first two months of treatment, necessitating interruption of chemotherapy. One of these (home) was found to have scabies. In the other three, the rash was considered to be due to PAS toxicity. Desensitization was successful, although it took more than five months in one case.

In summary, nine patients (five home and four sanatorium) developed manifestations which were considered at the time to be possible toxic reactions to PAS. Subsequent observation suggested that four, or at the most five (2.6%), of the 193 patients (one with jaundice and oedema, one with a rash and jaundice and three with a rash) had true hypersensitivity or toxic manifestations to PAS.

One patient (home) developed an acute confusional state seven days after the start of treatment. She was admitted to a mental hospital and made a rapid recovery despite the continuance of the isoniazid and PAS, as allocated; it was therefore considered that the confusional state had been coincidental and was not due to isoniazid toxicity. There was no other suspicion of isoniazid toxicity in either series.

The occurrence of rashes or jaundice as possible toxic manifestations of treatment was a disadvantage of the combination of isoniazid and PAS used in this study, since such occurrences raised problems of differential diagnosis and complicated the management of patients, whether the manifestations ultimately proved to be toxic or not. Moreover, patients were very quick to blame all untoward symptoms and signs on their medicine. In this connexion, it is of interest that the only patient who

absconded from the home series had attributed an attack of jaundice to his medicine.

PREGNANCY

Patients who were pregnant were not admitted to the study. However, during the 12 months, seven home patients (all in the main analysis) became pregnant. Of the seven, one aborted in the fourth month of pregnancy and six continued to full term. Of these six, three were under treatment for the full period of gestation, two were in the ninth month of pregnancy at the end of the 12 months of treatment and one was in the third month.

Since none of the sanatorium patients became pregnant, the occurrence of pregnancy in patients treated at home introduces a difference between the two series to the possible disadvantage of the latter.

LEPROSY

Although patients known to have leprosy were not admitted to the study, it was found in the course of the 12 months that six patients (two at home and four in sanatorium) were suffering from leprosy. They were investigated and treated in the Madras Government General Hospital as out-patients, with diaminodiphenylsulfone, alone or with chaulmoogra oil. They all appear in the main analysis.

DIABETES

Although diabetics were not knowingly admitted to the study, two patients, both in sanatorium, were discovered to have diabetes after admission to treatment. One is in the main analysis; the other appears in the subsidiary group with PAS resistance before treatment (section XIII, page 120).

SPECIAL HOSPITAL AND SANATORIUM ADMISSIONS

In the home series, complicating conditions, whether tuberculous or non-tuberculous, were usually treated on an out-patient basis. If the illness was serious, or special investigations or treatment not available to out-patients were required, then the patient was admitted to hospital. In all, 19 (20%) of the 96 home patients were admitted to hospital (or to sanatorium) at some time in the course of the 12 months. It was also necessary to admit six (6%) of 97 sanatorium patients to hospital for special investigations or treatment. The details are given in Table 34.

TABLE 34
SPECIAL ADMISSIONS TO HOSPITAL OR SANATORIUM

Diagnosis	Number of patients	Duration of in-patient treatment (days)
A. Admission of home patients to hospital (or sanatorium)		
1. Complications of pulmonary tuberculosis or its treatment :		
Severe dyspnoea	2 *	6, 8
Ischio-rectal abscess	1	7
Toxic hepatitis due to PAS	1 **	11
Bronchitis and cor pulmonale	1 **	16
Bronchopleural fistula and pyopneumothorax †	1 **	353
2. Non-tuberculous conditions :		
Normal confinement	3	2, 2, 5
Abortion	1	4
Menorrhagia	1	10+4
Carcinoma of oesophagus	1	18
Bacillary dysentery	1	22
Osteomyelitis of femur	1	23
Cataract	1	24
Microcytic anaemia	1	33
Chronic diarrhoea	1 **	35
Addisonian syndrome	1 **	10+60+7
Confusional state and bedsores †	1 **	24+82
Total patients admitted	19	
B. Admission of sanatorium patients to hospital		
Phymosis	1	1
Influenza	1	3
" Measles " (PAS rash)	1	9
" Chickenpox " (PAS rash)	1 **	12
Jacksonian epilepsy	1	13
Carcinoma of tongue	1 **	29
Total patients admitted	6	

* Including one patient not in the main analysis
** This patient was not in the main analysis.
† This patient was admitted to sanatorium as well as to hospital.

Six of the home series were in-patients for one week or less, a further eight for between one week and one month, and five for periods varying from one to 11½ months. Six of the admissions were for conditions attributed directly or indirectly to pulmonary tuberculosis or to the treatment. The remainder were for conditions unrelated to the tuberculosis. Only two of the home patients were admitted to sanatorium. Of the total of 19 in-patients, 12 are in the main analysis (see Table 34). The other seven feature in subsidiary analyses for a variety of reasons, but only one (with a confusional state and bed sores) was excluded from the main analysis solely on grounds of in-patient treatment for more than six weeks.

Turning to the sanatorium series, six patients were transferred to hospital for investigation or treatment, two for less than one week, and four for between one week and one month. Two of the patients, who were admitted to the Infectious Diseases Hospital, Madras, for observation for measles and chickenpox respectively, proved to be suffering from eruptions due to PAS, but the sanatorium regulations made it necessary to transfer them until the doubt was resolved. Of the six patients, four are in the main analysis.

In summary, it was necessary during the course of the 12 months to give in-patient treatment to 19 home patients and to admit to hospital six of the sanatorium patients. It may be concluded that when large numbers of patients are under treatment for many months, especially at home, it is essential to have access to a small number of hospital beds with facilities for general medical investigation and treatment, and to a lesser extent, to tuberculosis beds.

XI. SELF-ADMINISTRATION OF THE MEDICINE

Constant stress was laid on the necessity of taking the medicine regularly. Both in the Centre and at home, before the patient started treatment and also throughout the 12 months, the doctors, public health nurses, health visitors and social workers laid great emphasis on the importance of regularity in self-administration of the cachets, stressing this not only with the patient but also with the whole family. The procedures for checking whether the home patients were regular in taking their medicine evolved with increasing experience in the course of the study. Two methods were used—namely, urine tests for PAS and counts of the patient's stock of cachets, these latter being introduced systematically later in the study.

URINE TESTS

From the start of the study, whenever a patient attended the Centre, a urine specimen was collected for a ferric chloride test for PAS (Simpson, 1956). It became evident, however, that some patients took cachets in the morning before attending the Centre in order to ensure that the result of the urine examination would be satisfactory. Hence, urine specimens were then also collected at routine visits to the home. Subsequently it became evident that some patients were taking the cachets in anticipation of routine home visits, so, finally, completely unexpected visits were also paid at least once a month to collect a urine specimen, and this became the routine for the rest of the study. For the sanatorium patients, even though the standard practice was to watch the patients swallowing their cachets, a weekly urine specimen was tested for each patient, the day on which it was tested being changed once a month.

A preliminary study was undertaken on volunteers from the Centre's staff to investigate for how long, in Madras, the result of the urinary ferric chloride test would remain positive following a single standard dose of the combination of isoniazid plus PAS used in this study. In a series of 24 volunteers all the specimens were positive at one to three hours after taking the drug. The test was next performed on specimens collected between 12 and 14 hours after taking the drug, and 19 (79%) were positive. In 13 of the volunteers, a test was also performed at 18 hours, and the result was positive in 11 (85%). At 26 hours, eight (33%) of the 24 volunteers still yielded positive results and between 28 and 30 hours, six (25%) still had a positive result. In interpreting the results presented below, it should therefore be borne in mind that a negative result usually indicates that no PAS has been taken for at least 12 hours and often for considerably longer.

Table 35 summarizes the results of the ferric chloride tests for the patients in the main analysis, grouping the patients according to the number of months in which they produced one or more

TABLE 35

BACTERIOLOGICAL STATUS AT 12 MONTHS RELATED TO THE REGULARITY OF TAKING CACHETS OF ISONIAZID PLUS PAS (AS ASSESSED BY FERRIC CHLORIDE TESTS ON THE URINE)

Number of months with at least one negative result	Treatment series	Males				Females			
		total patients	bacteriological status at 12 months			total patients	bacteriological status at 12 months		
			quiescent	doubtful	active or relapsed		quiescent	doubtful	active or relapsed
0	Home	19	16	1	2 *	9	6	2	1
	Sanatorium	47	39	3	5	19	18	0	1
1	Home	8	7	0	1	8	7	0	1
	Sanatorium	2	2	0	0	8	8	0	0
2	Home	8	6	1	1	5	3	0	2
	Sanatorium	0	0	0	0	3	3	0	0
3	Home **	8	6	1	1	4	3	0	1 †
4	Home	3	2	1	0	1	1	0	0
5	Home	0	0	0	0	1	0	1	0
6	Home	0	0	0	0	2	1	0	1
7	Home	1	1	0	0	0	0	0	0
8	Home	0	0	0	0	0	0	0	0
9	Home	0	0	0	0	2	0	0	2
10	Home	0	0	0	0	0	0	0	0
11	Home	0	0	0	0	1	1	0	0
12	Home	0	0	0	0	0	0	0	0

* Including one patient who had tests in nine months, after which his chemotherapy was changed because he had deteriorated

** No patient in sanatorium gave negative results in three or more months.

† Including one patient who had tests in 11 months, after which her chemotherapy was changed because she had deteriorated

negative results to the ferric chloride test. The figures and the presentation in the table for the sanatorium series are tabulated only up to two months, since no patient in sanatorium gave a negative result in more than two of the 12 months.

Considering the males first, it can be seen that 19 (40%) of 47 home patients gave positive results throughout the 12 months, compared with 47 (96%) of 49 males in sanatorium. At the other extreme, 12 home patients (26%) gave one or more

negative results in at least three of the months, one of the 12 having negative results in no fewer than seven months, whereas no sanatorium male had negative results in more than one month. Turning to the females, 9 (27%) of 33 at home had positive results throughout the 12 months, compared with 19 (63%) of 30 females in sanatorium. At the other extreme, 11 (33%) had one or more negative results in at least three of the months, two of the 11 being irregular in six months, two in nine and one in 11 months; in contrast, in sanatorium no female patient gave negative results in more than two months. The average number of tests per month was higher for the home than for the sanatorium patients, being 5.2 for the home males, 5.3 for the home females, 4.2 for the sanatorium males and 4.3 for the sanatorium females. Despite this, it may be concluded that negative results were much more frequent at home than in sanatorium. They were also more frequent in the females than in the males, indicating that the females at home were less reliable in the self-administration of the cachets than the males.

It seems likely that the negative findings in the sanatorium patients were due, in part, to an initial difficulty which was experienced by the sanatorium staff with the end-point of the test; in part, also, to an occasional negative result in a patient whose last dose had been taken in the late afternoon of the previous day, so that an interval of more than 12 hours had elapsed before the urine specimen was collected for testing, which, in the sanatorium, was before the morning dose of cachets had been taken. It is also possible that some of these results represent occasions when the patients did not take their cachets, having escaped the direct supervision of the sanatorium staff. In the home series, on the other hand, it is much more likely that the negative results really indicated occasions or periods when patients were irregular in taking their medicine. Unlike the specimens in sanatorium, all the specimens obtained in the Centre or the home were collected within, at most, a few hours after the time when the patients should have taken the morning dose, so that any negative result was highly suggestive of the omission of at least one dose.

Table 35 also presents the bacteriological status at the end of 12 months in relation to the regularity with which the cachets were taken. The findings in sanatorium can be readily dismissed, since the two males and 11 females who gave negative results all attained bacteriological quiescence at 12 months. Turning to the home series, 19 of the males gave positive results throughout and of these, two (11%) had active disease at 12 months compared with three (11%) of 28 who gave at least one negative result. Of the females, nine gave positive tests throughout and one (11%) had active disease at 12 months compared with seven (29%) of 24 who gave one or more negative results. Thus, although there were no differences between the males there was a suggestion among the females that there was less likelihood of bacteriological quiescence in those who showed irregularity in taking their cachets. Further analysis revealed, however, that the females who were irregular were also, as a group, at a minor disadvantage in respect of the score for total extent of disease before treatment and in pretreatment sputum positivity, so that these findings may merely reflect an inferior clinical condition at the start of treatment among the female patients in whom irregularities occurred.

Table 36 sets out the irregularities in terms of the proportion of ferric chloride tests in the 12 months that showed negative results and their relationship to the bacteriological status at 12 months. Considering the males treated at home, 12 (26%) of 47 gave negative results in 5% or more of the tests and of these, one gave negative results in 16% of the tests. In sanatorium, only two (4%) of 49 males yielded negative results, in both cases to a single test. Among the females at home, 13 (39%) of 33 gave negative results in 5% or more of the tests and, of these, six gave negative results in 10% or more of the tests; indeed, three were negative in 21%, 35% and 36% of the tests respectively. In sanatorium, two (6%) females among 33 were in the 5%-9% category, both having yielded negative results in 5% of the tests. It may be concluded that the proportion of negative results for the home patients was much higher than for those in the sanatorium. Also, for the females at home the percentage of negative results obtained was higher than for the home males.

In interpreting these findings, it should be pointed out, first, that the great majority of the tests were performed on specimens collected at visits to the Centre after patients had learned that urine specimens would be tested for drug content. It is very likely that some patients, otherwise irregular, took medicine on the day of a visit to the Centre in order to produce a positive urine result, so that these findings are likely to underestimate the irregularity. Secondly, these findings were obtained

TABLE 36

BACTERIOLOGICAL STATUS AT 12 MONTHS, RELATED TO THE PROPORTION OF URINE EXAMINATIONS WHICH WERE NEGATIVE TO THE FERRIC CHLORIDE TEST

Percentage of tests with negative results	Males								Females							
	home				sanatorium				home				sanatorium			
	total	bacteriological status *			total	bacteriological status			total	bacteriological status			total	bacteriological status		
		Q	D	A		Q	D	A		Q	D	A		Q	D	A
0	19	16	1	2 **	47	39	3	5	9	6	2	1	19	18	0	1
1-4	16	13	1	2	2	2	0	0	11	10	0	1	9	9	0	0
5-9	11	8	2	1	0	0	0	0	7	4	0	3 †	2	2	0	0
10-14	0	0	0	0	0	0	0	0	2	0	1	1	0	0	0	0
15-19	1	1	0	0	0	0	0	0	1	1	0	0	0	0	0	0
20 or more	0	0	0	0	0	0	0	0	3	1	0	2	0	0	0	0
Total	47	38	4	5	49	41	3	5	33	22	3	8	30	29	0	1

* Q = Quiescent ; D = Doubtful ; A = Active or relapsed

** Including one patient who had tests in nine months, after which his chemotherapy was changed because he had deteriorated

† Including one patient who had tests in 11 months, after which her chemotherapy was changed because she had deteriorated

in a Centre where the whole staff laid the greatest emphasis on the importance of regularity in medicine-taking to the patient, his family and neighbours (Fox, 1958). There was no clear-cut evidence that negative results during treatment and bacteriologically active disease at 12 months were associated.

CACHET COUNTS

Planned visits were paid to the home, and the cachets were often counted. In the later months, in addition, cachet-counting at surprise visits was also introduced. The findings at a count were usually recorded as being correct, or as an excess or a deficit, the number in excess or deficit being noted before adjusting the patient's stock of cachets to the correct number. Occasionally the records merely noted an irregularity without indicating its nature.

Apart from the two males who died, the cachets were checked on a total of 1156 occasions for the 47 males during the 12 months—an average of 2.0 checks per month. For the 33 females, 1001 checks were carried out—an average of 2.5 per month. The total number of discrepant cachet counts was 76 (6.6%) for the males and 91 (9.1%) for the females. Of these, an excessive number of cachets was found on 52 (4.5%) occasions for the males and 54 (5.4%) occasions for the females. Too few cachets were found on 17 (1.5%) occasions for the males and 11 (1.1%) occasions for the females. On seven occasions in the males and 26 occasions in the females there was a discrepancy, but the case records do not report whether an excess or a deficit was found. Assuming that the proportions of excesses and deficits in these unspecified discrepancies were the same as those in the specified discrepancies, the estimated total of occasions on which too many cachets were discovered was 57 (4.9%) for the males and 76 (7.6.%) for the females, and the estimated total of deficits was 19 (1.6%) for the males and 15 (1.5%) for the females. The counting of the cachets thus provides additional evidence that the females more often failed to take their cachets as prescribed than did the males.

The results of a further analysis to investigate the size of surpluses are set out in Table 37. Considering the surpluses first, of 52 examples in the males, 46% consisted of an excess of up to four cachets—that is, of a single dose for patients weighing 100 lb. or more ; in 27% the inaccuracy was five to eight cachets, in 4% nine to 12 cachets

TABLE 37

THE NUMBER OF SURPLUS CACHETS RECORDED AT COUNTS MADE AT VISITS TO THE PATIENTS AT HOME

Number of surplus cachets	Counts for males		Counts for females	
	number	%	number	%
1- 4	24	46	23	43
5- 8	14	27	14	26
9-12	2	4	7	13
13-16	6	12	4	7
17-20	1	2	2	4
21 or more	5	10	3	6
Unspecified	0	0	1	2
Total recorded surpluses	52	101	54	101
Number of patients with recorded surpluses	25		22	

in excess were found and in 12%, 13 to 16. In all, six male patients (12%) had excesses of more than 16 cachets (representing at least two days' supply), the excesses being 17, 23, 28, 48, 49 and 64. Turning to the females, in 43% of 54 examples a surplus of up to four cachets was found, in 26% there were five to eight, in 13% nine to 12, in 7%, 13 to 16 excess cachets. In all, four female patients had an excess of more than 16 cachets on a total of five occasions, the excesses being 17 and 48 for one patient and 20, 22 and 42 for the other three. Thus, although surpluses were more frequently found in the female patients, occurring in 22 (67%) of 33 compared with 25 (53%) of 47 males, the size of the surpluses was very similar for both males and females. On only five occasions (in five different patients, three males and two females) was a surplus of 40 or more cachets found (which represents nearly a week's supply). It will be appreciated that such a number indicates a practically complete stoppage of self-administration of medicine, since the patient received a weekly supply of cachets which varied in number from 42 to 56, dependent on the body-weight of the patient at the time. The deficits, which are a puzzling finding (but which indicate, at least, that the medicine was not being taken as prescribed), were of up to four cachets in 22 instances (12 in males and 10 in females) and between five and eight cachets in six instances (five in males and one in a female).

An analysis (not tabulated) was undertaken to compare the bacteriological status at the end of 12 months, for the males in whom a surplus of cachets was found on one or more occasions, for the males whose counts were always regular, and for those for whom only deficits or unspecified inaccuracies were recorded. There was no evidence that bacteriological status was associated with these irregularities. A corresponding analysis for the females led to similar conclusions.

In summary, inaccuracies in the cachet counts were detected in 6.6% of checks on males and 9.1% of checks on females, being found in 28 of 47 males and 25 of 33 females. The inaccuracy was usually a small one, but in five patients (three males, two females) it was large enough to suggest that the patient had completely stopped taking the medication. There was no evidence to show that patients who yielded inaccurate counts fared less well than those for whom the counts were always accurate. In considering these data, it should be appreciated that cachet-counting has definite limitations, for some patients with the correct number of cachets were found, at the same time, to have a negative test, suggesting that they were, in fact, disposing of the cachets other than by consuming them.

XII. VARIOUS SOCIAL FACTORS

In section II of this report it was stated that treatment at home meant that, as a group, the patients concerned had a poorer diet, less rest, took the cachets less regularly, and had inferior accommodation and less nursing than the sanatorium patients. Except for the last, which is self-evident, studies have been undertaken which have confirmed all these differences, and the findings (apart from those on self-administration of the medicine—see section XI) are given in the present section. In addition, some details of employment, the income of the patient and of the family, and the financial assistance which the families in both series received are also reported in this section, since these background factors of the study

merit careful consideration. Finally, the major sociological problems which arose in both series of families are described.

DIET

A special study of the diet of the patients, both before the start of treatment and during its course, was undertaken to investigate what differences, if any, existed between the home and sanatorium series. The diet before the start of treatment was assessed for all the patients in both series in the main analysis. In addition, for the first 116 patients in the main analysis, an assessment was undertaken at some time in the second six months of treatment. In the remaining patients—namely, the last 46 admitted to treatment in the main analysis—a more detailed investigation was undertaken, and diet assessments were obtained at six weeks, and at three, six, nine and 12 months.

The diets were studied by the oral questionnaire method, following the standard procedure in current use in the ICMR Nutritional Research Unit (Gopalan, personal communication, 1957). In addition, a weightment assessment of the diet was undertaken at three months on the 46 patients under detailed investigation to confirm the reliability of the oral questionnaire. The data will be the subject of a separate report and they are therefore referred to only briefly here.

The results of the assessments before the start of treatment were similar for patients in the home and sanatorium series. An analysis of the oral questionnaire results during treatment, however, shows that there were then major differences between the diet in the home and the sanatorium series. Considering the males first, 19 (42%) of 45 home patients for whom results were available had a daily intake of less than 2000 calories, compared with 2 (4%) of 48 sanatorium males. This difference is statistically significant at the 0.1% level. For the females, the corresponding proportions were 20 (61%) of 33 at home, compared with one (3%) of 30 in sanatorium. This difference is also significant at the 0.1% level. At the other extreme, there were six home patients, all male, who claimed a daily intake of more than 3500 calories, compared with none in the sanatorium series. Despite this small group, it is evident that, as a series, the home patients, both male and female, were at a major disadvantage in respect of total calorie intake. It must also be noted that the patients at home were physically more active than those in sanatorium (see page 107), and that this accentuated the inferiority of the calorie intake of the home patients.

Turning to the *total* protein content of the diet, 20 (44%) of 45 males at home were receiving less than 50 g total protein a day, compared with none of 48 males assessed in the sanatorium. This difference is statistically significant at the 0.1% level, as is the difference between the females, in whom the corresponding proportions were 20 (61%) of 33 and none of 30. Further, the *animal* protein content of the diet was less than 30 g in 38 (84%) of 45 home males, compared with none of 48 in the sanatorium series, and in 32 (97%) of 33 home females, compared with none of 30 in sanatorium. These differences between the home and sanatorium series are also significant at the 0.1% level. The daily intake of animal protein of 30 of the patients treated at home (16 males and 14 females) was less than 10 g.

Most of the assessments of diet for the two series were undertaken over a calendar period of some six months. Hence, the differences observed do not represent differences at a particular point of time when, by chance, the sanatorium patients were on a favourable diet and the home patients were on an unfavourable diet. The detailed investigations on the last 46 patients in the main analysis have also confirmed that major dietary differences persisted throughout the 12 months. It may be concluded that the home series was at a very considerable disadvantage dietetically compared with the sanatorium series throughout the 12 months of treatment.

In assessing the diet, allowance has been made for the powdered milk which was given to all the families in the study; this did not appreciably diminish the differences between the two series. It is also evident that the financial assistance given to a proportion of the families of patients treated at home (see page 114 et seq.) still left major differences between the two series in respect of diet.

REST AND ACTIVITY

The general policy which was adopted for rest and activity for the home patients was, if possible, to persuade them to rest all the time for the first month or two. As their general condition improved they were allowed to undertake some slight activity. Within a month or two of sputum conversion they were permitted to undertake part-time activity. Full-time activity was usually resumed within three or four months of sputum conversion, although it was sometimes delayed if sputum conversion had occurred particularly early—that is, in the first or

TABLE 38
ASSESSMENT OF THE PATIENTS' ACTIVITY DURING THE 12-MONTH PERIOD

Home

patient's activity	males 3 months No.	%	males 6 months No.	%	males 9 months No.	%	males 12 months No.	%	females 3 months No.	%	females 6 months No.	%	females 9 months No.	%	females 12 months No.	%
Resting	13	*27*	2	*4*	2	*4*	1*	*2*	11	*33*	3	*9*	2	*6*	1	*3*
Slight	29	*60*	29	*60*	18	*38*	8	*17*	16	*48*	14	*42*	6	*18*	2	*6*
Part-time	5	*10*	15	*31*	18	*38*	20	*43*	5	*15*	15	*45*	22	*67*	14	*44*
Full-time	1	*2*	2	*4*	9	*19*	17	*37*	1	*3*	1	*3*	3	*9*	15	*47*
All patients**	48	*99*	48	*99*	47	*99*	46	*99*	33	*99*	33	*99*	33	*100*	32	*100*

Sanatorium

patient's activity	males 3 months No.	%	males 6 months No.	%	males 12 months No.	%	females 3 months No.	%	females 6 months No.	%	females 12 months No.	%
Complete bed-rest	0	*0*	1	*2*	0	*0*	0	*0*	0	*0*	0	*0*
Up to toilet only	18	*37*	6	*13*	0	*0*	6	*20*	1	*3*	0	*0*
Up two hours	27	*55*	36	*75*	39	*81*	20	*67*	26	*87*	27	*90*
Up four hours	4	*8*	5	*10*	9	*19*	4	*13*	3	*10*	3	*10*
All patients †	49	*100*	48	*100*	48	*100*	30	*100*	30	*100*	30	*100*

* This patient was under investigation in hospital for a carcinoma of the oesophagus.

** Excluding throughout one male patient who died in the second month, at nine and 12 months one who deteriorated and had his chemotherapy changed; also excluding at 12 months one who died in the seventh month, and at 12 months one who deteriorated and had her chemotherapy changed; also excluding throughout one female patient who died in the first month; also excluding at 12 months one female patient who deteriorated and had her chemotherapy changed

† Excluding throughout one male patient who died in the first month, one at six months only and one at 12 months (both discharged from sanatorium at the time of the assessment); also excluding throughout one female patient who died in the first month

second month of treatment. It was, however, often not possible to adhere to this policy. Some patients insisted on returning to work early, a few refused to stop work at all and some had no work to which to return. Also, the home patients did not usually rest as much as advised. Contrary to instructions, the great majority, unless actually feeling ill, would sit or potter about at home much of the day and often go for walks. It was sometimes possible to arrange for relatives to undertake the duties of a housewife who was under treatment, but many housewives, because of their family responsibilities, were unable to restrict their activity for very long, if at all.

The majority of home patients attended the Centre weekly from the very start of treatment for a supply of medicine; the drugs were delivered to the home only for the very ill patients. This meant that, on at least one day a week, the home patients had to travel a distance of up to five miles each way, usually on foot because they could not afford fares.

In sanatorium, the position was different. Here complete bed-rest with bed-pan facilities was available for the very ill patients, and ill patients remained in bed, getting up for toilet only. The activity of all the patients remained restricted throughout the 12 months, the maximum time that a patient was officially allowed up being four hours a day. Activity was, however, not rigidly restricted, and individual patients were undoubtedly up for longer than was officially permitted. In addition, after the completion of six months' treatment, sanatorium patients were allowed to go home for 12 hours on one day a month, provided that they were sufficiently fit.

Table 38 sets out the assessment of the activity at three, six, nine and 12 months for the males and females at home, and at three, six and 12 months for the males and females in sanatorium. (For the sanatorium series there was so little change between six and 12 months that the figures at nine months have not been tabulated.) Considering the males at home, it will be seen that at three months 13% of 48 had returned to part-time or full-time activity. This proportion increased to 35% at six months, to 57% at nine months and to 80% at 12 months. There was thus a progressive increase in the activity of the male patients at home over the period. In contrast only a small proportion of the male patients in sanatorium—namely, 8% of 49 at three months, increasing to 19% at 12 months—were officially up for four hours a day. The proportion of male patients officially up for two hours a day also

steadily increased. The contrast between the females at home and in sanatorium was equally striking, for the proportion engaged in part-time or full-time activity at home was 18% of 33 at three months, 48% at six, 76% at nine and 91% at 12 months; of the sanatorium females 13% of 30 were up for four hours a day at three months; the corresponding proportions officially up for four hours a day at six months and at 12 months were each 10%.

Comparing the sexes in the home series, it can be seen from Table 38 that the women tended to return to part-time or full-time activity more rapidly than the men. Thus, at six months 16 (48%) of 33 women, compared with 17 (35%) of 48 men,were undertaking part-time or full-time activity. At nine months, the corresponding proportions were 76% of 33 women and 57% of 47 men, and at 12 months 91% of 32 women and 80% of 46 men. It is likely that this difference arises because the women were usually housewives and therefore under pressure to return to their domestic duties; a number of the men, on the other hand, were unemployed and therefore able to take more rest. There was also some hesitancy on the part of the Centre's medical staff to allow the men to return to their normal occupations, which were frequently very strenuous and involved long hours (see page 111).

It is difficult to equate activity at home with activity in sanatorium, but it is very unlikely that the maximum amount of activity undertaken by any of the sanatorium patients represented as much as part-time activity in the home patients, even allowing for the fact that some of the sanatorium patients were undoubtedly up for longer than their officially permitted time. It may be concluded that the patients in the home series were physically much more active in the course of the 12 months than those in the sanatorium series.

ACCOMMODATION

Before the patients were admitted to treatment, details of the living accommodation used by the families were recorded, including measurements of the floor areas of all the rooms and also the covered verandah, if part of the family's accommodation. The details were recorded by the health visitor in charge of the patient and were checked at the first home visit by a doctor. The Environmental Hygiene Committee of the Government of India has recommended that the floor area of living rooms should not be less than 50 sq. ft (4.6 m^2) per person and that, unless mechanical replacement of air is provided for, there should be at least 500 cu. ft (14.2 m^3) of space per person (India, Ministry of Health, 1950). If either of these conditions is not satisfied, overcrowding exists.[1]

The area per person has been calculated for the families of the home patients. The accommodation has been taken as that occupied by the household on the day of admission of the patient to the study. The household was defined as all those who shared the same living accommodation and the same kitchen on that day. However, anyone who was living within the household on that day but not throughout the period of three months immediately before or three months immediately after the admission of the patient has been regarded as a visitor and excluded from the calculation (this did not apply to births within three months before, or deaths within three months after, the day of admission). Finally, the area per person was calculated according to two definitions. According to Definition 1, each member of the household counted as one person, irrespective of age. According to Definition 2, infants under the age of one year were not counted, children between the ages of one and 10 years were counted as one half, and household members aged 10 years or more counted as one person.

The findings are shown in Table 39. According to Definition 2 (the less stringent), 69% of the 47 families of male patients at home and 84% of the 33 families of female patients at home had less than 45 sq. ft (4.2 m^2) per person, and so were indisputably overcrowded ; in addition, two patients (both male) had no home and lived on the street. On the other hand, 11 families (nine (19%) of the male patients and two (6%) of the female patients) had 55 sq. ft (5.1 m^2) or more per person and may thus be considered to have had an adequate area per person. There is an intermediate group of seven families (four of male patients, three of female patients), which had an area of between 45 and 54 sq. ft per person, in which it is difficult, on the basis of area alone, to be certain whether or not there was overcrowding according to the Environmental Hygiene Committee's definition. No attempt has

[1] The Environmental Hygiene Committee makes other recommendations which, had they been used as criteria in this report, would increase the proportions of families classed as overcrowded. Appendix IV of the Committee's report refers to minimum standards of accommodation recommended by six other Committees in India, all of which lay down higher standards.

TABLE 39

THE AREA OF LIVING ACCOMMODATION PER PERSON IN THE FAMILIES OF THE PATIENTS TREATED AT HOME, AT THE TIME OF ADMISSION TO TREATMENT

Area per person (square feet) *	Number of families							
	by Definition 1 **				by Definition 2 **			
	male patient in study		female patient in study		male patient in study		female patient in study	
	number	%	number	%	number	%	number	%
Homeless	2	4	0	0	2	4	0	0
5-14	3	6	6	18	2	4	4	12
15-24	15	32	16	48	12	26	12	36
25-34	13	28	3	9	12	26	8	24
35-44	4	9	5	15	6	13	4	12
45-54	3	6	3	9	4	9	3	9
55 or more	7	15	0	0	9	19	2	6
Total †	47	100	33	99	47	101	33	99

* 1 sq.ft = 0.09 m^2

** Definition 1 : For the purpose of calculating the area per person, each member of the household counted as one person.

Definition 2 : For the purpose of calculating the area per person, infants under one year were not counted, each child between one and 10 years counted as one half, and each member of the household aged 10 years or more counted as one person

† The families of two male patients who died are excluded from this table; the area per person was in the 25-34 sq.ft group for one family and in the 45-54 sq.ft group for the other, according to both definitions.

been made to invoke the second half of the Committee's definition referring to the volume of air, but the great majority of dwellers in the local type of Indian hut, even if they have an area of 50 sq. ft per person, are very unlikely to have 500 cu. ft of air per person. The walls of these huts are very rarely as high as five feet (1.5 m) ; the roof then slopes upwards to a peak which is rarely as high as 12 feet (3.7 m) from the ground. Hence, the figures, since they ignore volume, tend to underestimate the degree of overcrowding as well as the number of families overcrowded. Moreover, in calculating the area per person, the area of covered verandahs has been included with that of the actual living-rooms, even though covered verandahs often cannot be used as living accommodation during the monsoon period.

During the course of the 12 months, 18 families, 15 of whom had been overcrowded, changed their accommodation, in four cases more than once. The first change of accommodation was studied for these 18 families ; for 12 the new accommodation provided a greater area per person, for one the area was unchanged and for five the area was smaller, one of these families becoming overcrowded as a result of the move. Thus, changes in the accommodation during the 12 months tended to increase the area per person. Even so, of the 15 who had been overcrowded in their first home, 11 were still overcrowded in their second home, and one was overcrowded by Definition 1, although now in the 45-54 sq. ft group by Definition 2.

Few changes in the household membership took place during the 12 months of treatment. Births and deaths were infrequent, and only a few radical changes occurred, as, for example, when there was a family quarrel or when a group of relatives joined the household.

In contrast to the home series, the sanatorium patients were treated in airy, well-ventilated wards in a sanatorium in the country.

It may be concluded that the great majority of the home families were living in overcrowded conditions, the female patients being at a greater dis-

advantage than the males. The accommodation for the sanatorium patients was clearly superior.

OCCUPATION AND ECONOMIC STATUS

The economic status of the patient and the family at the time treatment started will be dealt with in detail as part of a separate socio-economic report. For the purpose of the present report, however, it is necessary to give a general picture of the occupations of the patients and the economic status of the patients and the families at the start of treatment, and also to study the impact of the disease and its treatment on the income level of the patient.

Occupation

A broad classification of occupations is set out in Table 40 for the male and female patients. Since the majority of the female patients were house-

TABLE 40

OCCUPATION OF THE MALE AND FEMALE PATIENTS AND OF THE GUARDIANS OF THE FEMALE PATIENTS

Occupation	Number of patients	Male patient		Female patient		Guardian of female patient	
		home	sana-torium	home	sana-torium	home	sana-torium
Non-earning :							
Unemployed	5	2	3	0	0	0	0
Housewife	47	—	—	23	24	0	0
Student	4	2	2	0	0	0	0
Nun	1	0	0	0	1	0	0
Earning :							
Craftsman (e.g., electrician, mason, potter, tailor, weaver)	29	14	13	2	0	4	7
Heavy unskilled labourer (coolie) (e.g., building labourer, cart-puller, ganger)	8	5	3	0	0	10	4
Light unskilled labourer (e.g., cleaner, messenger, peon, sweeper)	19	6	11	2	0	5	2
Petty shopkeeper, street vendor, salesman	11	6	5	0	0	0	4
Domestic servant (e.g., ayah, cook)	9	4	2	1	2	1	1
Food and produce handler (e.g., foodstall holder, milkman, poultryman)	9	0	2	4	3	5	3
Government employee (e.g., fireman, policeman, post office worker)	0	0	0	0	0	3	3
Cotton mill operative	4	1	3	0	0	0	0
Driver	1	0	1	0	0	3	3
Printing worker	0	0	0	0	0	1	1
Other trade (e.g., barber, dhobi)	3	1	2	0	0	1	0
Clerical	4	4	0	0	0	0	1
Student (earning)	1	0	1	0	0	0	0
Professional (teacher, tutor)	3	1	1	1	0	0	0
Landlord	1	1	0	0	0	0	0
Total *	159	47	49	33	30	33	29 **

* Two male patients at home and one male and one female patient in sanatorium who died are excluded from this table; the two males at home were an electrician and a coolie respectively, the male in sanatorium was unemployed (retired), and the female in sanatorium was a housewife, her husband being a heavy unskilled labourer.

** The nun has been regarded as having no guardian.

wives, the occupation of the guardian (usually the husband) of each female patient (except one, a nun) has also been tabulated, to show the occupation of the chief or sole earner in the families of these patients. It can be seen from the table that the majority of male patients in employment fell into five groups—namely, craftsmen, heavy unskilled labourers, light unskilled labourers, vendors and domestic servants. Many of the male patients, especially the craftsmen and those in heavy unskilled occupations, worked very long hours in tropical conditions. Few of the male patients were in sedentary occupations, and only six were classified as professional or clerical. Many of the patients were employed on casual labour. Only 15 of the 63 female patients were earning, the majority of these being petty shopkeepers, or in domestic occupations. The female patients who were earning also had responsibilities in their homes.

Income of the patients before and during treatment

It was very difficult to make an accurate assessment of the income of the patients, since there was often considerable reluctance to divulge this information. Moreover, in Madras, in the section of the community under study, income often varies from month to month because there is much casual employment. In this study the families remained under observation for a 12-month period, and there were repeated opportunities to inquire about the patients' incomes. Also, as the months went by, the patients and families became increasingly friendly and confiding towards the Centre's staff, and it is believed that the information on income became progressively more trustworthy. The sources of information available to the staff were the patient, the family, employers, landlords, neighbours and friends. The social workers, the health visitors, and, to a lesser degree, the medical staff had frequent contact with such sources because of the active interest taken in the welfare of the family, in the patient's return to work, and in the employment of other family members. This has enabled a reasonably reliable picture to be built up of the financial status of the patients.

The earning capacity of many of the patients under study declined over a period of several months before the start of treatment. A number attended the Centre for the first time when they had been off work for weeks or even months, and when they had already run into debt because of their loss of earning capacity. Hence, the income at the time of admission to treatment is misleading as a means of classifying the patients according to income status. Instead, the highest monthly income in the six months immediately preceding the start of treatment has been used, as this gives a much better indication of the normal income of the patient. However, being the highest monthly income in a six-month period, it tends to exaggerate the patient's earning capacity. It will be seen from Table 41 that the highest monthly income in the six pretreatment months for the male patients was, on average, Rs 48.31 [1] for those at home and Rs 47.27 for those in sanatorium. Four home and five sanatorium patients had not been earning for at least six months, two in each series being students. Only seven home and nine sanatorium patients had earned more than Rs 75.00. Of these, three patients (one at home and two in sanatorium) had earned Rs 100.00 and only one patient (home) had earned more—namely, Rs 120.00. As already stated, the majority of the women in each treatment series—that is, 23 of 33 at home, and 24 of 30 in sanatorium—were solely occupied as housewives and were not earning.

Apart from financial assistance from the Centre, which is detailed later in this section, some patients in each series received money from various sources during the course of treatment, consisting of gratuities and bonuses from the Madras Corporation, the State Government or private firms, unemployment sickness benefits through the Employees' State Insurance Scheme, rents, sale of property, and regular cash gifts from relatives. In addition to such sources of income, a number of the home male patients returned to work during the 12 months and again earned an income. Table 41 also shows the average of the monthly income during the 12 months of treatment for the home and sanatorium males and the income for the twelfth month for the home males. The figures for the females in the two groups have not been given since only five in the home group and one in sanatorium received any money at all during the 12 months.

The position for the males in sanatorium was comparatively straightforward. Twelve patients received money from one of the sources indicated above, having an average monthly income of Rs 14.64—that is, Rs 3.58 per month for each of the 49 males in sanatorium. This sum is very much

[1] Rupees 4.80 = US $1.00

TABLE 41

THE INCOME OF THE PATIENTS BEFORE AND DURING TREATMENT *

Income (in rupees per month) **	Highest monthly income in the six months immediately preceding the start of treatment				Average monthly income of male patients during the twelve months of treatment		Income of male home patients in the twelfth month of treatment
	males		females		home patients	sanatorium patients	number of patients
	home	sanatorium	home	sanatorium			
0	4	5	23	24	16	37	21
Less than 15	1	2	2	3	14	7	3
15 -	1	3	3	2	7	2	2
25 -	4	5	4	1	5	2	8
35 -	8	6	0	0	1	1	2
45 -	12	8	0	0	1	0	6
55 -	8	8	1	0	1	0	1
65 -	2	3	0	0	0	0	1
75 or more	7	9	0	0	2	0	3
Total †	47	49	33	30	47	49	47
Average per patient	Rs 48.31	Rs 47.27	Rs 7.12	Rs 2.83	Rs 14.77	Rs 3.58	Rs 23.01
Average per earning patient	Rs 52.81	Rs 52.64	Rs 23.50	Rs 14.17	Rs 22.39	Rs 14.64	Rs 41.60

* Excluding financial assistance given by the Centre

** Rs 4.80 = US $1.00

† Two home (male) and two sanatorium patients (one male, one female) who died are excluded from this table.

less than the average of the highest monthly income in the six months before the start of treatment, which was Rs 52.64 for the 44 earning male patients —that is, Rs 47.27 for all 49 male patients. There was thus, inevitably, a major fall in income among the sanatorium patients.

Turning to the home series, the position is clearly different, since a number of male patients returned to work during the course of the 12 months. Even so, 16 (34%) of 47 males received no income from any source during the 12 months. The remaining 31 had an average monthly income of Rs 22.39, representing an average of Rs 14.77 for the whole group of 47 patients. These figures are considerably higher than the corresponding figures for the sanatorium series, and it is evident that it was possible for the home series to maintain some earning capacity over the 12 months. These earnings were, however, considerably lower on average than the usual income of the patients.

A further analysis was undertaken to see to what extent the earning capacity of the male patients in the home series had been restored by the end of the 12 months, and the income for the twelfth month is presented in Table 41 with this aim. It will be seen that 21 patients were still unemployed, and that the remaining 26 patients received an average of Rs 41.60, which is not greatly below the average monthly pretreatment income for those who had been earning in the home series (Rs 52.81). On the other hand, the average income of the 47 patients, as a group, was Rs 23.01—that is, less than half the pretreatment income for the series. It is of interest to review the reasons why 21 patients were not earning at 12 months, compared with only four before treatment. One was a student, one had been unemployed for 10 years before the start of treatment and throughout treatment, seven were unsuccessfully trying to find work, one was being very selective in the choice of a job and one was frankly avoiding

work. There remain 10 patients who were not earning on account of their medical condition. Of these, five were sputum-positive, one was suffering from asthma, two, though sputum-negative, were still in poor general condition and too frail to work, and one patient, who had been referred back to his firm by the Centre as fit to work, was being kept off work by the firm's doctor. Finally, for one patient the Centre's doctors delayed the return to work because a positive sputum, graded as 2-plus both on smear and culture, was obtained at the eighth month, although it proved later to have been an isolated positive result. Of the four who had been unemployed before the start of treatment, two were in employment at 12 months ; one of the students had become a salesman and the other patient, who had never previously worked, was a vaccinator's assistant.

Income of the families before treatment

An assessment of the total family income at the start of treatment is given in Table 42. The family income recorded is the sum of the highest monthly income of the patient in the six months immediately prior to admission to treatment and the monthly income from any source of all the other family members at the time when the patient was admitted to treatment. It can be seen that, considering the families of male patients, 28 (62%) of 45 treated at home had monthly incomes of less than Rs 100.00, as did 33 (67%) families of 49 males in sanatorium. The corresponding figures for the females were 30 (91%) of 33 at home and 24 (83%) of 29 in sanatorium. Only four (9%) of families of the home males, five (10%) of the families of the sanatorium males, none of the families of the home females and two (7%) of the families of the sanatorium females had incomes of more than Rs 150.00. Only two families—of a home male (Rs 212.00) and of a sanatorium female (Rs. 270.00)—had a monthly income of more than Rs 200.00. It may be concluded that the total incomes for the families of the patients under study were, in the main, low. Further, the data indicate that, on average, the families of the male patients, both at home and in sanatorium, had larger incomes than the families of the female patients.

A knowledge of the total family income is of limited value unless it is related to the size and to the age- and sex-composition of the family. With this in view, each family has been expressed in terms of standard units, an adult male being equivalent to one standard unit; an adult female (15 years or over) was taken as 0.8, and a child under the age

TABLE 42

THE TOTAL FAMILY INCOME BEFORE THE START OF TREATMENT

Income (in rupees per month) *	Male patient in study		Female patient in study	
	families of home patients	families of sanatorium patients	families of home patients	families of sanatorium patients
Less than 30	1	2	1	0
30–	5	6	10	8 **
50–	12	10	11	8
70–	10	15	8	8
100–	13	11	3	3
150 or more	4 **	5	0	2
Total families †	45	49	33	29

* Rs 4.80 = US $1.00

** Including one family with two members in the study; each entry in the table refers to the index case; the contact was a male patient at home

† The families of two male patients at home, and one male and one female patient in sanatorium, who died, have been excluded; another female sanatorium patient, a nun, who had no family or income, has also been excluded.

of 15 years as 0.6 standard unit. These ratios were adopted from a previous study in India (India, Ministry of Commerce, 1949). The total income of each family was then expressed as the income per standard unit, and the findings are presented in Table 43.

It will be seen that, considering the families of males first, 12 (27%) of 45 at home and 16 (33%) of 49 in sanatorium had an income per standard unit of less than Rs 20.00 per month and that only four (9%) at home and five (10%) in sanatorium had an income of Rs 50.00 or more per unit. Considering the families of female patients, 18 (55%) of 33 at home and 19 (66%) of 29 in sanatorium had an income of less than Rs 20.00 per standard unit; none of the families at home and two (4%) of the families of sanatorium patients had an income of more than Rs 50.00 per unit. It will be appreciated that the income per unit is derived from the total family income, which in these families is spent mainly on food.

An indication of the purchasing power of the income per standard unit is given by the sum which was spent by the Madras Government on food for the patients in the sanatorium series. Rs 1.84 daily was spent for the non-vegetarian patients and Rs 1.66 daily for the vegetarian patients—that is, Rs 55.20 for a 30-day month for the non-vegetarians and Rs 49.80 for the vegetarians. These sums are based on bulk purchases of food for an institution with over 600 patients, so that it is very unlikely that a patient treated at home would be able to purchase the same with an identical daily expenditure. Also, Chaudhuri (1959), when referring to the current cost of living in India, wrote: "At present price levels, a balanced diet for one adult costs at least Rs 1.50 a day (Rs 45.00 a month); and the minimum total requirement, including food and clothing, is about Rs 60-70 per month."

FINANCIAL ASSISTANCE TO THE FAMILY

The present study, as mentioned earlier, entailed keeping the patients under treatment for a full 12 months, about half of them at home and half in sanatorium. When the study was planned it was regarded as essential, in order to undertake it at all, to have funds available to give financial assistance to espe-

TABLE 43

THE TOTAL FAMILY INCOME BEFORE THE START OF TREATMENT, EXPRESSED IN TERMS OF STANDARD UNITS*

Income per standard unit (in rupees per month) **	Male patient in study		Female patient in study	
	families of home patients	families of sanatorium patients	families of home patients	families of sanatorium patients
0–	1	3	6	4
10–	11	13	12	15 †
20–	15	18	9	6
30–	9 †	9	5	1
40–	5	1	1	1
50–	2	1	0	2
60 or more	2	4	0	0
Total families ††	45	49	33	29

* An adult male (15 years or over) was counted as one standard unit, an adult female (15 years or over) as 0.8 of a standard unit and children below 15 as 0.6 of a standard unit.

** Rs 4.80 = US $1.00

† Including one family with two members in the study; each entry in the table refers to the index case; the contact was a male patient at home

†† The families of two male patients at home, and one male and one female patient in sanatorium, who died, have been excluded; another female sanatorium patient, a nun, who had no family or income, has also been excluded.

cially needy families for the bare necessities of food, or for their rent. This was particularly so because it was evident that patients under study would, in the main, be drawn from the lower income-groups or the unemployed. Also, it might often be necessary to treat the chief or sole earner of the family in sanatorium for 12 months, a circumstance which could only cause the other members of the family financial hardship. In addition, it was thought that funds would be required for a number of miscellaneous items, e.g. to pay fares for very ill patients to attend the Centre. The ICMR therefore provided a welfare fund, and this proved invaluable. The Centre had a full-time social worker and, later, an assistant social worker as well, and they and the doctors, public health nurses and health visitors all co-operated in assessing financial need. The actual payments to the families were made by the social workers.

Table 44 sets out the number of months in which the families of patients in the two series received financial assistance from the Centre's welfare fund. Considering the males, the families of 34 (76%) of 45 at home, compared with 28 (57%) of 49 in sanatorium, received financial assistance, and it was given in more than six of the 12 months to 26 (58%) of the home families and 22 (45%) of the sanatorium families. Considering the females, 20 (61%) of 33 home families, compared with 10 (33%) of 30 sanatorium families, received financial assistance. In all, assistance was given for the full 12 months to the families of seven males at home and six in sanatorium, three females at home and two in sanatorium. It may be concluded that the families of sanatorium patients stood in less frequent need of financial assistance than the families of home patients, presumably largely because one member was being cared for in sanatorium, and that in

TABLE 44

THE NUMBER OF MONTHS IN WHICH FAMILIES RECEIVED FINANCIAL ASSISTANCE FROM THE CENTRE'S WELFARE FUND DURING THE 12-MONTH PERIOD

Number of months in which payments were made	Male patient in study				Female patient in study			
	families of home patients		families of sanatorium patients		families of home patients		families of sanatorium patients	
	number	%	number	%	number	%	number	%
0	11	*24*	21	*43*	13	*39*	20	*67*
1-3	2	*4*	0	*0*	4	*12*	1	*3*
4-6	6	*13*	6	*12*	7	*21*	3	*10*
7-9	8 *	*18*	7	*14*	2	*6*	2	*7*
10-12	18	*40*	15	*31*	7	*21*	4 *	*13*
All families **	45	*99*	49	*100*	33	*99*	30	*100*
Total families receiving financial assistance	34	*76*	28	*57*	20	*61*	10	*33*

* Including one family with two members in the study; each entry in the table refers to the index case; the contact was a male patient at home

** The families of two male patients at home, and one male and one female patient in sanatorium, who died, have been excluded.

both series more frequent assistance had to be given if the study patient was a male.

Six males at home and four in sanatorium, and six females at home and eight in sanatorium, had a contact who had tuberculosis, also under treatment at the Centre for at least a part of the 12 months. In addition, one female at home and one male in sanatorium had two contacts under treatment for tuberculosis. In some instances it was necessary to give a greater amount of financial assistance for a longer period to a family if more than one member had tuberculosis.

Table 45 shows the average monthly payment during the 12-month period to the families of male and female patients in the two series. Among the male patients the average payment to the 34 home families which received financial assistance was Rs 12.71 per month, compared with an average of Rs 10.17 per month for the 28 sanatorium families which were assisted. The corresponding figure for

TABLE 45

THE AVERAGE MONTHLY SUM PAID AS FINANCIAL ASSISTANCE TO FAMILIES FROM THE CENTRE'S WELFARE FUND DURING THE 12-MONTH PERIOD

Average payment (in rupees per month) *	Male patient in study				Female patient in study			
	families of home patients		families of sanatorium patients		families of home patients		families of sanatorium patients	
	number	%	number	%	number	%	number	%
None	11	*24*	21	*43*	13	*39*	20	*67*
Under 3.00	1	*2*	2	*4*	10	*30*	5	*17*
3.00-4.99	4	*9*	4	*8*	0	*0*	0	*0*
5.00-9.99	12	*27*	11	*22*	6	*18*	2	*7*
10.00-14.99	10	*22*	8	*16*	4	*12*	1	*3*
15.00-19.99	1	*2*	1	*2*	0	*0*	2 **	*7*
20.00 or more	6 **	*13*	2	*4*	0	*0*	0	*0*
All families †	45	*99*	49	*99*	33	*99*	30	*101*
Average payment for the families receiving assistance	Rs 12.71		Rs 10.17		Rs 5.34		Rs 7.63	
Average payment for all families	Rs 9.61		Rs 5.81		Rs 3.24		Rs 2.54	

* Rs 4.80 = US $1.00

** Including one family with two members in the study; each entry in the table refers to the index case; the contact was a male patient at home

† The families of two male patients at home, and one male and one female patient in sanatorium who died, have been excluded.

the families of the 20 female patients in the home series which were assisted was Rs 5.34 per month, compared with Rs 7.63 per month for the 10 assisted families of females in sanatorium. Taking into account all the families under study—whether or not they received financial assistance—the average monthly payment to families of male patients was Rs 9.61 for those at home and Rs 5.81 for those in sanatorium. The corresponding sums for the families of female patients were Rs 3.24 and Rs 2.54 respectively. Of those receiving assistance, 11 families of the male patients (five at home and six in sanatorium) and 15 families of female patients (10 at home and five in sanatorium) received an average of less than Rs 5.00 a month. On the other hand, eight families, all of male patients (six at home and two in sanatorium), received in all more than Rs 20.00 per month. Of these, only three families received more than Rs 30.00—namely, Rs 46.58 and Rs 36.25, respectively, for two in the home series, and Rs 31.50 for one in the sanatorium series. Both the home patients had a second family member under treatment for tuberculosis in the Centre; the sanatorium patient had two contacts under treatment. It may be concluded that it was possible to keep the financial assistance to a modest level, but that more assistance had to be given when male patients were under treatment, whether at home or in sanatorium.

It will be appreciated that the financial assistance, which for the families of home patients averaged Rs 12.71 per month for males and Rs 5.34 per month for females receiving financial assistance, was small. An indication of its purchasing power is given by comparing it with the expenditure on diet alone for the sanatorium patients, which was about Rs 50 per month (see page 114) or with Chaudhuri's estimate that the minimum total requirements for an adult to meet the current cost of living in India, are "about Rs 60-70 per month" (Chauduri, 1959). Moreover, it is certain that, in the great majority of cases, the financial assistance benefited not merely the patient but the whole family. Taking this into account, the actual benefit to the patient from the financial assistance was even less than the sum might suggest.

It was sometimes necessary, in addition, to give money for fares to patients in the home series to enable them to attend, or return home from, the Centre. It will be appreciated that, on occasion, money given for fares will have been used for other purposes, possibly even to buy food, and, conversely, that money paid to families as financial assistance will sometimes, no doubt, have been used for fares. In all, payments for fares were made to a total of 16 of 80 home patients (10 males, six females). For six of these, payments were made in a single month, and for only five patients were payments made in more than three months ; one of these patients (male) received payments for a total of seven months. A total of Rs 131.63 was paid for fares to patients in the home series during the 12-month period—Rs 57.75 to the males and Rs 73.88 to the females. This is an average of Rs 0.48 each month per male patient who received fares, and Rs 1.03 each month per female patient. When expressed as an average for the entire home series, the monthly disbursement was Rs 0.10 per male and Rs. 0.19 per female.

It is of interest to consider some of the reasons why money was paid for fares. One patient (male), who received a total of Rs 28.00, had his chemotherapy changed because of radiographic deterioration, and therefore had to travel to the Centre, a distance of nearly four miles each way, for a daily streptomycin injection; the payments for fares were all made after the course of streptomycin started. Two patients, who received Rs 30.00 and Rs 9.06 respectively, were pregnant, and attended the clinic regularly with an escort; the payments were for rickshaws for the patients and their escorts. Another patient, who received Rs 14.00 during the course of the 12 months, was suffering from anaemia due to menorrhagia and was not considered fit to walk to the Centre and back home. These four patients between them received Rs 81.06—substantially more than half the total amount spent in fares for the whole home series. In assessing the sum spent on fares, it should be mentioned that very ill patients were brought to the Centre and taken home by ambulance, if necessary, so that other resources were available for the conveyance of these patients to and from the Centre.

DISRUPTION OF FAMILY LIFE

Throughout the period of the study the whole clinical staff of doctors, health visitors and public health nurses, as well as the social workers, were very much concerned with the welfare of the patients and their families. Every effort was made to encourage the families to report their problems to the Centre, and, if possible, to resolve them. The families of the sanatorium patients were perhaps seen less

frequently than those at home, but never less than once a month, and the families receiving financial assistance attended weekly for the payment. It proved possible to establish very friendly relations with the majority of the families in both series, and, as a result, a great deal of sociological information was obtained and recorded in the social workers' records.

In this subsection are summarized the major sociological problems which arose in the families in both series in the course of the 12 months, or shortly afterwards. It will be appreciated that sometimes, in the sanatorium series, a difficulty not always apparent during the 12 months in sanatorium matured shortly after the patient was discharged. As a result, in considering family problems no attempt has been made to adhere rigidly to the period of 12 months, as has been done throughout the rest of this report. The two series have been observed equally after the 12 months and no bias between the series is introduced by admitting sociological information from early in the second year.

To obtain the data considered in this subsection, the social workers' record for each family was discussed at a meeting of the social workers with all the clinic doctors, public health nurses and the senior health visitor. Every family was discussed, to be sure that the sociological difficulty was a real one and that nothing of which the Centre's staff was aware was being overlooked.

It will be appreciated also that a sociological problem in a family was not necessarily due to the disease or its treatment, whether the patient was at home or in sanatorium. Some of the difficulties would very likely have occurred in the life of a family not afflicted by tuberculosis. It is nevertheless legitimate to compare the difficulties which arose, because the marital status of the patients under treatment was very similar for the two series. The respective numbers at home and in sanatorium were 35 and 31 husbands, 27 and 25 wives, three widowers (in each series), six and five widows, 23 and 30 bachelors, and two and three spinsters.

There were major problems in 8 (8%) of the 96 families in the home series. The wife of one patient deserted him and their children to join another man, and a second patient was deserted by her husband. There were three families which split, and there were three serious family quarrels, in two of which it was felt that the quarrel had made it very difficult for the patient to rest as much as had been recommended.

Turning to the sanatorium series, there were major problems in 20 (21%) of the 97 families. There were six instances of infidelity and in three of these the difficulties have persisted since the patient's discharge from sanatorium; these marriages must at present be considered as definitely split. In one family the husband (who was the patient) suspected the wife of infidelity. In another, the husband suspected the wife (who was the patient) of infidelity while she was in sanatorium. In each of these families the spouses at present only live together for part of the time, so that these marriages are at least partially split. There was one further example of an atmosphere of serious suspicion between the husband and wife; this arose during the course of sanatorium treatment, but resolved when the husband returned home at the end of 12 months. There were five cases in which one family member deserted the home. One family split, and the husband became a nomad until the wife was discharged from sanatorium. In the remaining five cases the absence of the patient from the home led to difficulties within the family. With the possible exception of one family which was disputing the ownership of property, it seems unlikely that the particular difficulty would have arisen had the patient been treated at home. Of the above problems, four were responsible for the premature discharge of the patient from sanatorium.

There is little doubt that, *in this study*, many more sociological difficulties arose in the family life of the sanatorium patients, and that they were graver than those occurring in the home series. It also seems likely that many of the problems were directly due to the fact that the patient was in sanatorium, and might never have occurred if the patient had been treated at home. On the other hand, some of the difficulties reported in the home series might have been avoided if the patient had been treated in sanatorium. It may be concluded that, *in this study*, the treatment of patients in sanatorium for a period of 12 months carried sociological disadvantages.

SUMMARY OF SOCIAL FACTORS

It has been shown in this section that, although the two series had similar diets before allocation to treatment, the home series was at a serious dietary disadvantage throughout the 12 months, especially in respect of total protein and animal protein. The home series also had less rest, and returned to activity more rapidly, than the sanatorium series.

The majority of the patients in the home series were treated in overcrowded accommodation, and the patients in both series were very largely drawn from the lower income-groups. Financial assistance from the Centre's welfare fund was at a modest level for the families of both series of patients. Major sociological problems arose more frequently in the families of patients treated in sanatorium than in those of the home patients. Apart from this last factor, this study of a standard chemotherapy in home and sanatorium patients thus represented a comparison of treatment under good conditions in sanatorium with treatment under poor conditions in the home.

XIII. SUBSIDIARY GROUPS OF PATIENTS NOT INCLUDED IN THE MAIN ANALYSIS

This section reports on a total of 14 home and 16 sanatorium patients who were separated from the main analysis for a number of reasons (see Table 2, page 61). Some patients appear in more than one subsidiary group because they exhibited two or even three of the characteristics under separate analysis; each patient's clinical progress is, however, described once only.

PATIENTS WITH ISONIAZID-RESISTANT ORGANISMS BEFORE TREATMENT

Nine patients had isoniazid-resistant organisms when treatment began. All were interrogated on several occasions during the course of treatment, as their relationship of trust with the Centre's staff became more and more firmly established, to discover whether they had had previous chemotherapy and were concealing the fact. Two admitted that they had had previous chemotherapy which, it was believed, had included isoniazid. The duration of chemotherapy was uncertain, but was probably for a period of at least three weeks in one patient (who also had a streptomycin-resistant strain) and three months in the other. For the remaining seven patients no history of previous chemotherapy was obtained, and it is considered that these seven patients (3.6% of the 192 with pretreatment results available) had been infected with isoniazid-resistant organisms—that is, had primary isoniazid resistance. It should be emphasized that every effort was always made to discover whether a patient had had previous anti-tuberculosis chemotherapy. Thus, dispensary cards from other hospitals and prescriptions from private doctors were scrutinized. In addition, relatives and, where appropriate, friends were approached, and, if necessary, private doctors who had seen the patients before start of treatment were contacted.

The two patients (both home) who had had previous chemotherapy had positive bacteriological results at every month throughout the 12-month period; both developed PAS resistance, one at one month and the other at six months.

Of the seven patients regarded as having primary isoniazid resistance, three (one home, two sanatorium) responded satisfactorily to treatment, being bacteriologically quiescent at 12 months by the definition adopted in this report (see page 77); one became sputum-negative at two months, another first became negative at one month but produced an isolated positive culture at six months (with organisms still resistant to isoniazid but sensitive to PAS), and the third became negative at the third month, apart from two colonies, sensitive to both drugs, which grew at eight months. Two patients responded badly bacteriologically; one (sanatorium) remained positive throughout the 12 months and yielded PAS-resistant organisms from seven months onwards; the other (home) was positive for three months, then negative for three months, but had positive results at seven, 10 and 12 months, the organisms still being resistant to isoniazid but sensitive to PAS. One patient (home) died after 22 days of treatment. Finally, the seventh patient (home) developed a bronchopleural fistula and a pyopneumothorax 10 days after starting treatment, and was admitted to sanatorium. She received the allocated isoniazid and PAS, and daily streptomycin in addition, for the whole 12 months, but at the end of that time still had an unexpanded lung. The sputum was consistently negative from two months onwards.

In sum, both patients who had had previous chemotherapy fared badly. Two of seven patients with primary resistance also fared badly, but three responded well. It was not possible to assess what influence the isoniazid resistance had on the course of the disease in the remaining two, since one died shortly after starting treatment and the other received triple drug therapy following an early complication. It may be concluded, however, that the progress of

the patients in this small subsidiary group compared unfavourably with that of the patients in the main analysis. These cases and their contacts will be reported in detail elsewhere.

PATIENTS WITH PAS-RESISTANT ORGANISMS BEFORE TREATMENT

Six patients had PAS-resistant organisms before the start of treatment. Subsequent interrogation revealed a history of previous chemotherapy in one of these, who was believed to have had at least a month of treatment which included PAS. The other five patients (2.6% of the 192 patients with pretreatment results available) were considered to have been infected with PAS-resistant organisms—that is, they had primary PAS resistance.

The patient (home) who had had previous chemotherapy developed a major hypersensitivity to PAS shortly after starting treatment; when three attempts to desensitize him had failed, his chemotherapy was changed after two months to daily streptomycin plus isoniazid, which he received for the remainder of the 12-month period. His sputum became negative at five months and remained negative for the remainder of the 12-month period.

Of the five patients with primary PAS resistance, three (two home, one sanatorium) fared well. All three were bacteriologically quiescent at 12 months; one became negative at two months and the other two at three months, and all three remained so for the remainder of the 12-month period. In all three the organisms were still sensitive to isoniazid at the last positive culture. A fourth patient (sanatorium) remained positive throughout the 12 months and yielded isoniazid-resistant organisms from three months onwards. The fifth patient (home) became jaundiced in the fifth week of treatment. He attributed this to his medication and himself arranged for his admission to a sanatorium, where he had streptomycin plus isoniazid for five months. He was sputum-negative at the end of the 12 months. In summary, of four patients with primary PAS-resistant organisms who received isoniazid plus PAS throughout the 12 months, three were quiescent bacteriologically at the end of the period, and the fourth was persistently sputum-positive.

PATIENTS WITH SENSITIVE ORGANISMS WHO HAD HAD MORE THAN TWO WEEKS OF PREVIOUS CHEMOTHERAPY

There were four patients with organisms sensitive to the two drugs before treatment, from whom a history of chemotherapy prior to admission to the study was subsequently obtained. One patient (home), who had had three weeks of intermittent streptomycin and daily isoniazid before treatment, was sputum-negative by the third month, but at five months yielded one colony resistant both to isoniazid and to PAS, and at nine months five colonies resistant to isoniazid but sensitive to PAS. By the definition adopted in this report, this patient was bacteriologically quiescent at the end of the 12 months. One patient (sanatorium), believed to have had six weeks of intermittent streptomycin and daily isoniazid, was bacteriologically negative by four months, produced two colonies at six months, resistant to isoniazid but sensitive to PAS, and was bacteriologically quiescent at 12 months. One patient (sanatorium) was believed to have had a month of streptomycin plus PAS followed by six weeks of PAS alone. He became bacteriologically negative at two months and remained so, except for an isolated positive culture at nine months which was resistant to isoniazid and sensitive to PAS. In the later months of treatment, however, gross excavation of a previously radio-opaque lung occurred, and the cavitation, which had been slight on admission, was graded as extensive at the end of 12 months; the over-all radiographic change from 0 to 12 months was reported as "slight deterioration". The fourth patient (home), who was believed to have had two months of isoniazid alone prior to his admission to the study, remained positive bacteriologically throughout the 12 months, having organisms resistant both to isoniazid and to PAS from the fourth month onwards. In sum, of four patients, two attained quiescence, one remained positive bacteriologically and the fourth had a gross excavation of the lung, although this was not associated with a positive sputum. This experience, though limited, seems unfavourable in comparison with that in the main series.

NON-TUBERCULOUS DEATHS FROM DISEASES WHICH INFLUENCED THE COURSE OF THE TUBERCULOSIS

Two patients, one in each series, were separated from the main analysis because they died of non-tuberculous conditions, which it was considered might well have had an unfavourable influence on the course of their tuberculosis.

The home patient died in the ninth month of treatment. The patient had recurrent diarrhoea,

weakness and low blood-pressure (90 mm/60 mm) and was admitted to the Government General Hospital, Madras, on three occasions, where a diagnosis of Addison's disease was made. He received cortisone for two months and, in view of the diarrhoea, the PAS was stopped and he had streptomycin for 39 days together with isoniazid. There was a temporary improvement which he failed to maintain, and he died in hospital. At post-mortem examination there was evidence of healing tuberculosis of the lungs (the sputum had been negative for two months), there being some small apical nodules in the left lung and two small epithelializing cavities in the right lung. The adrenal glands were normal. The outstanding finding was intense congestion of the mucosa of the intestines and the colon. The skull was not opened. The immediate cause of death was an acute enteritis, but the patient's tuberculosis had been responding to treatment. The cause of the Addisonian-like syndrome was not satisfactorily established.

Shortly after admission to treatment, the sanatorium patient was found to have had a carcinoma of the tongue, and died in the eighth month. The patient had shown moderate radiographic improvement at six months, and all the cultures were negative from two to six months. At seven months, however, by which time the patient was in a serious clinical condition, the sputum became positive again, both on smear and on culture.

PATIENTS WITH FAILURE OF DESENSITIZATION, OR PROLONGED DESENSITIZATION, TO PAS

Desensitization to PAS failed in one home patient (see page 120). One sanatorium patient developed a rash, due to PAS, in the fourth week of treatment and desensitization took nearly five months, during which time he received streptomycin in addition to isoniazid and the desensitizing doses of PAS. For this reason he was separated from the main analysis. The sputum was negative at two months and remained so for the rest of the 12-month period, apart from an isolated positive culture at six months.

PREMATURE DISCHARGES FROM TREATMENT

Much difficulty was encountered in persuading many of the patients to remain in sanatorium for the full 12 months, despite considerable generosity on the part of the sanatorium authorities in the interpretation of the regulations and the most strenuous efforts on the part of the Centre's medical and nursing staff and social workers to induce patients to complete their treatment. In cases of need, financial assistance was given to the families, and fares for relatives to visit the sanatorium, as well as many small privileges for the patients. Despite all these efforts, 12 patients (10 males, two females) left the sanatorium in the course of the 12 months, three for disciplinary reasons, the other nine absconding.

The females who absconded were both readmitted one day later. Another patient, who was discharged in the seventh month, was followed up in the Centre, and completed an uninterrupted 12 months of chemotherapy at home. A fourth patient was readmitted to sanatorium one month after being discharged for disciplinary reasons. A fifth, who absconded in the third month, was admitted to another hospital in Madras City, where he continued his allocated chemotherapy for five months and was then readmitted to the sanatorium for the remainder of the 12-month period. These five patients were all retained in the main analysis in the sanatorium series.

There remain seven sanatorium patients (7%) who were not included in the main analysis. Two left sanatorium in the third month, one in the fourth, two in the fifth, one in the sixth and one in the seventh month. All were visited and efforts were made to persuade them to continue treatment at the Government Tuberculosis Institute, Madras; three did and four did not. Of the three who did, one received treatment with isoniazid and PAS for the rest of the 12 months, one received isoniazid and intermittent streptomycin for six months and the third received three months of PAS alone. At the end of the 12 months, all seven patients were persuaded to attend the Centre for re-examination. Of the seven, three (two of whom had received no further chemotherapy after discharge) were bacteriologically positive, one still having organisms sensitive to isoniazid and PAS, another having a strain resistant to isoniazid and sensitive to PAS, and the third a strain resistant to both drugs. Thus, at the end of the 12 months, all seven patients were alive but three were still infectious, two with resistant organisms—an unfavourable experience compared with the main series of patients who remained in the sanatorium.

In contrast, only one patient absconded from treatment in the home series. This was the patient with primary PAS resistance who developed jaundice after five weeks, which he attributed to his treatment (see pages 99 and 120).

It was thus much more difficult to ensure that the sanatorium patients, especially the males, stayed in sanatorium than to persuade patients to remain under treatment at home. This is the reverse of what had been predicted before the start of the study by every authority, both in India and Europe, with whom the project was discussed at the planning stage.

HOSPITAL OR SANATORIUM STAY OF MORE THAN SIX WEEKS FOR HOME PATIENTS

Three home patients had a long stay in hospital—that is, a stay of more than six weeks. Two of these have already been reported (see pages 119 and 120). The third patient developed bed sores during a three-week stay in a mental hospital, and was admitted to sanatorium, where she remained for 11 weeks until they were healed. The last positive culture was isolated from this patient at two months; she had bacteriologically quiescent disease at 12 months.

SUMMARY

In all, 14 patients allocated to treatment at home have been considered in this section. Four of the 14 patients had bacteriologically active disease at 12 months and there were two deaths (one being non-tuberculous). This experience, although small, is rather worse than that of the main home series, in which 13 of 82 patients had bacteriologically active disease at 12 months, seven were bacteriologically of doubtful status and there were two deaths (one being non-tuberculous).

Of the 16 patients who had been allocated to treatment in sanatorium, five had bacteriologically active disease at 12 months, another had developed gross cavitation of the lung, although the sputum was still negative, and there was one non-tuberculous death. The other nine patients were classed as bacteriologically quiescent, but for four of them this was based solely on results at 12 months—that is, on less stringent criteria than those adopted throughout the rest of the report. This experience is worse than that of the main sanatorium series, in which six of 81 patients were bacteriologically active, three were bacteriologically of doubtful status, and there were two deaths.

Considering both series together, the progress of patients who did not conform to the basic criteria of having sensitive organisms before treatment, of having had no previous chemotherapy and of following the prescribed regime uninterruptedly for the 12 months, was poorer than that of patients who had conformed to these criteria.

XIV. DISCUSSION

The present report is mainly concerned with the results of the comparison of treatment of patients for a period of 12 months at home or in sanatorium. It will be appreciated that there is comparatively little information, obtained from controlled clinical trials, on the value of chemotherapy either in the tropics or in under-developed countries, apart from the hospital studies reported from East Africa (Hutton et al., 1956; Fox et al., 1956; Howells & Swithinbank, 1957; East African/British Medical Research Council Sulphone Investigation, 1959), and from India (Frimodt-Møller, 1949, 1955; Frimodt-Møller et al., 1953, 1954). Furthermore, a review of the world literature has revealed that few controlled studies of the relative value of bed-rest and ambulation in the treatment of pulmonary tuberculosis have so far been reported. Wier et al. (1956, 1957) reported an eight-month comparison of modified bed-rest and ambulation in sanatorium patients in the USA. Tyrrell (1956) compared sanatorium treatment with ambulant treatment at home for a period of three to six months in patients from Glasgow. The Research Committee of the Tuberculosis Society of Scotland (1957) reported interim results of a study of chemotherapy and bed-rest at home or in hospital for a minimum period of three months, in comparison with the same chemotherapy in patients permitted to lead their normal working life. Acutely ill patients were not admitted to these studies, which are hardly comparable with the present investigation, in which the great majority of the patients had moderately advanced or far advanced disease, all had symptoms, and many were clinically ill, a number seriously so (see Appendix). Furthermore, treatment was for a period of 12 months and, in addition, is being continued at home for a second 12 months for patients in both series in order to investigate relapse and its pre-

vention. Finally, the social conditions of our patients were very different from those in the American and British inquiries.

For the present study it was decided to use a standard form of oral chemotherapy—namely, isoniazid 200 mg daily together with PAS (sodium salt) 10 g daily, for patients weighing 100 lb. (45 kg) or more. The dosage was reduced for lighter patients, and ranged from 3.7 to 6.6 mg/kg bodyweight for isoniazid and from 0.19 to 0.33 g/kg for PAS (sodium). The drugs were given together in the same cachet and were prescribed in two doses daily. This combination was chosen because it is administered orally ; it is known to be efficacious ; it is not associated with a high incidence of side effects or toxic manifestations ; and because it has been used in controlled clinical studies, so that much is known about it in relation to other regimes (Great Britain, Medical Research Council, 1953b, 1955 ; Bowerman, 1957 ; East African/British Medical Research Council Sulphone Investigation, 1959). The combination was given to the patients in both series, so that the essential comparison was of treatment at home with treatment in sanatorium for 12 months, the patients receiving the same standard chemotherapy throughout this period.

In all, 96 patients were allocated to treatment at home and 97 to treatment in sanatorium, by a process of randomization. Of these, 82 at home and 81 in sanatorium form the basis of the main analysis in this report. These were the patients who had organisms sensitive to both drugs at the start of treatment, maintained that they had had no previous antituberculosis chemotherapy, or chemotherapy for less than two weeks (despite questioning on several occasions during treatment), and followed the prescribed course of treatment for the full 12 months.

Although the process of randomization was strictly observed, important pretreatment differences were, in the event, found between the two series of patients. The differences were in respect of the extent of cavitation and the total extent of disease radiographically, and in the bacterial content of the sputum. Although slight chance differences in pretreatment condition are to be expected in studies based upon random allocation of treatment, large differences in important criteria, as in the present study, represent a most unusual occurrence. The pretreatment differences have complicated the analysis of the present data. Since the disparity was greater for females than for males it has been necessary in this report to present the results separately for the males and females in the two series, and, in addition, to make special investigations of the influence of the pretreatment differences on the response to treatment in the two series. The risk of such differences might be reduced in future studies, especially if a wide range of disease types is being studied, by classifying the patients on the basis of the radiographic appearances and then allocating treatment at random within each class.

The most important finding is that even though the 49 *males* in the home series were at a disadvantage in respect of the radiographic features and bacterial content of the sputum when treatment started, as compared with the 50 males in sanatorium, there was little to choose between the progress of the males in the two series over the 12-month period. The sanatorium patients gained much more weight, as might have been expected, and the response of the erythrocyte sedimentation rate was greater. Nevertheless, the radiographic and bacteriological responses, which are the important assessments, show at most only a slight benefit to the sanatorium series. At the end of 12 months, 10% of the patients in each series had bacteriologically active disease, on the basis of very stringent criteria.

Because of the major pretreatment differences already referred to, it is less easy to interpret the direct comparison of the results of the treatment for *females* in the two series. These results showed definite radiographic and bacteriological disadvantages to the 33 treated at home, compared with the 31 in sanatorium. When allowance was made for pretreatment differences by statistical standardization, the radiographic responses were similar in the two series, but the bacteriological disadvantage to the females at home persisted. Taking these findings into consideration, it has been concluded that any difference which may exist between the response to treatment at home and the response to treatment in sanatorium for females in similar clinical condition before the start of treatment is small.

Summarizing the position for both sexes together, it is apparent that treatment at home gave results closely approaching those of treatment in sanatorium and that the differences between the results of home and sanatorium treatment were surprisingly small.

It should be noted that these satisfactory findings in the home patients have been obtained even though

the majority had major lesions, and that a high proportion had unfavourable clinical features when treatment began. The patients who did not attain bacteriological quiescence had, in the main, extensive disease and cavitation. It seems very likely that if it were possible, either as a result of mass radiography, or of propaganda directed at the general public and the medical profession, to diagnose the disease in its earlier stages, the results of domiciliary treatment might be even better than those reported here. It is also possible that better results could be obtained, even with a group of patients as ill as those in the present study, if the chemotherapy were changed to another combination when patients appeared unlikely to convert their sputum to bacteriological negativity on isoniazid plus PAS.

It has generally been considered that a good diet, satisfactory accommodation, adequate rest and nursing care together make an important contribution to the treatment of tuberculosis, and that they represent advantages of sanatorium treatment. In the present study, the patients treated at home were at a major disadvantage in all these respects but, despite this, they fared remarkably well; these factors appear to have had little influence on the results of treatment.

It has been established that there were major differences between the two series of patients in respect of diet during the course of the 12 months, the sanatorium diet being balanced and clearly superior. It will be possible, when the data have been analysed in detail, to study whether the attainment of bacteriological quiescence or the persistence of active disease is related to the diet of the patient. It is, however, already apparent that despite diets which were deficient in important factors, notably the protein content, the patients at home, as a group, made good progress. On the other hand, the control group in sanatorium, despite having a balanced diet, with an adequate protein content, and making substantial weight gains, derived surprisingly little additional benefit. The role of diet in the attainment of ultimate cure, however, has still to be investigated.

It has also been shown that the accommodation of the majority of the home patients not only before but during treatment was very unsatisfactory, a high proportion living in conditions of overcrowding. In addition, the home patients, especially the females, had less rest and returned to active work earlier. These further differences, which are usually regarded as predisposing to an unfavourable response to treatment, also do not appear to have affected the outcome to an appreciable extent.

An advantage of treatment in sanatorium is that the administration of medicines can be supervised, and, apart from major toxicity, no difficulty with the administration of medicine was encountered in the present study. However, an unexpected problem arose in persuading the home patients to take the medicine regularly, especially once they felt well. This occurred even though great emphasis was laid on the importance of regularity by all the clinical staff and although most patients attended the Centre regularly for their weekly supplies of medicine and their monthly examinations. In order to supervise the self-administration of the medicine, urine tests for PAS were introduced, and also counts were made of the patients' stock of cachets to see that the correct number remained. The most valuable checks by both methods were those made at surprise visits to the home. Although there was good evidence that a number of the patients were irregular in taking their medicine, it has not been possible to show that this was associated with clinical disadvantages during the 12-month period; however, the possibility of subsequent clinical disadvantages still remains to be studied. But even if moderate irregularities are ultimately shown to carry little long-term disadvantage, there must obviously be some level of intake below which irregularities do become important. Thus, in any scheme for domiciliary treatment depending on the self-administration of medicines, particular emphasis should be laid on the importance of regularity in taking them. Moreover, the present study has shown that mere regularity in attendance at a clinic does not necessarily mean that the patient is co-operating by taking his medicine. Difficulty with the self-administration of a combination of isoniazid and PAS in Britain has been reported by Simpson (1956), Dixon, Stradling & Wootton (1957), and Wynn-Williams & Arris (1958).

In contrast to these disadvantages of treatment at home, two unexpected advantages became apparent during the course of the study. The first advantage of treatment at home *in this study* was sociological. A detailed and careful sociological record was kept for each family. Whereas major problems were encountered in eight of the 96 home families, they arose in 20 of the 97 sanatorium families. Moreover, the sociological difficulties in the families of sanatorium patients were usually more serious than those in the families of patients treated at home. For example, there was one case

of infidelity in the home series, but in the sanatorium series there were six cases, anda suspicion of infidelity of a spouse in three more. There is little doubt that the long-term sanatorium treatment of patients *in this particular study* proved disruptive to family life, and this must be considered a disadvantage of treatment in the sanatorium series.

The second advantage concerns the co-operation of the patients. When this study was being planned, the general consensus of expert opinion, both in Europe and India, had been that it would be very difficult to obtain the co-operation of a high proportion of any group of patients in treatment at home, even for as long as three months, but that patients would welcome treatment in sanatorium. In the event, only one of the 96 patients allocated to treatment at home, compared with seven of the 97 patients admitted to sanatorium, was lost from treatment during the 12 months. In five more sanatorium patients there were interruptions in the sanatorium stay, although these did not necessitate the exclusion of the patients concerned from the main analysis. It proved much more difficult to persuade male patients to remain in sanatorium than female patients, 10 of the above 12 sanatorium patients being males. This difficulty in persuading patients to remain under treatment in sanatorium for a long period of time, despite a very active welfare service for the patients and their families, must be considered a major disadvantage of the sanatorium treatment. However, without the highly organized domiciliary service which concentrated on persuading patients to attend, especially when there were signs that they were becoming inattentive to treatment, it is certain that in this study a considerable proportion of the home patients would have stopped treatment.

In view of the poverty of the patients and their families and the need to keep their co-operation, a limited amount of financial assistance was given to more than half the families, as the main earner in the family often had to remain off work for several months or in sanatorium for a full 12 months. This financial assistance to the families was never above a modest level. As might have been expected, the families of male patients in both series needed more financial assistance than the families of female patients, and more assistance was required for the families of patients at home than for those of patients in sanatorium. It seems likely that this assistance contributed to the good co-operation of both series of patients, although it did not succeed in preventing the losses from sanatorium.

The conclusion from the present study that (except for some of the most severe cases) it is possible to obtain good results, at least for a period of 12 months, from treatment at home has practical implications. Provided it can be shown that relapse is infrequent and that there is no special risk to contacts if patients are treated at home, and provided that the results of this study would apply in other communities, there may be little to gain from admitting the general run of patients to sanatorium. There would still remain, however, a need to admit selected cases for in-patient care—for example, gravely ill patients, patients suffering from complications such as haemoptysis or spontaneous pneumothorax and those needing special management, such as pregnant patients and those for whom it is decided that surgery is necessary. The management of the more seriously ill patients who were treated at home in this study would certainly have been easier in sanatorium, since this would have given greater control over the patient and his treatment. If domiciliary treatment is embarked upon on a large scale, it would also appear essential to have access to a small number of hospital beds for non-tuberculous conditions. In the present study it became necessary to admit 13 (13%) of the home patients to hospital, mostly for short periods only, for the investigation or treatment of such conditions.

It cannot be assumed that any routine tuberculosis clinic would automatically obtain results approaching those reported here. The experience of this Centre suggests that certain minimum facilities are necessary for the satisfactory organization of an efficient domiciliary service based on a tuberculosis clinic. Among these facilities are an adequate supply of medication, and alternative medicaments for patients who are not responding satisfactorily; enough staff to supervise the patients, including a social worker and a public health nurse; an efficient appointment system, so that it is known when patients have failed to attend; adequate transport for the senior clinical staff to visit ill patients, or patients whose co-operation is flagging; an ambulance for ill patients; a small number of hospital beds for special or emergency cases; an organized system of surprise visits to the home to collect specimens of urine to test for the presence of the drug and to check the stocks of medicine; a laboratory capable of performing, as a minimal requirement, large numbers of reliable smear examinations of sputum for tubercle bacilli; and the resources to give at least limited financial assistance in cases of

particular need, since a proportion of patients will present in a destitute condition. Without adequate facilities and close supervision of the patients, the results of domiciliary treatment might well fall far below those reported here.

Toxic and hypersensitivity manifestations were infrequent in this study, occurring in only 2.6% of the total of 193 patients; all were attributable to PAS. This accords with other experience with this combination of isoniazid and PAS (Great Britain, Medical Research Council, 1953b, 1955; Bowerman, 1957; Tuberculosis Society of Scotland, Research Committee, 1957). Although the incidence is low, the occurrence of manifestations which were possibly toxic in origin complicated the management of patients, especially under domiciliary conditions, since patients at home were only too ready to blame all untoward symptoms on their medicine. The only patient lost from the home series during the 12 months discharged himself because he developed jaundice, which he attributed to the medicine.

The patients and their relatives were interrogated about previous chemotherapy on several occasions during the course of treatment, and other detailed inquiries were often made. After excluding any patients who might possibly have had previous antituberculosis treatment, primary drug resistance was found to isoniazid in 3.6% of all the patients, to PAS in 2.6% of patients, and to streptomycin in 2.2% of patients. Despite the difficulty in establishing the facts with certainty, it is believed that no patient who had had previous chemotherapy is included in these percentages. The figures may be compared with those obtained in the National Drug Resistance Survey in Great Britain (Fox et al., 1957), which used the same methods of sensitivity testing and had the same criteria of resistance; that survey reported an incidence of primary drug resistance to isoniazid in 0.7% of patients, to PAS in 2.2% and to streptomycin in 2.3% in Great Britain in 1955-56. It should be noted that the incidence of isoniazid-resistant strains was considerably higher in Madras in 1956-57 in the patients under study. In addition to such patients with primary drug resistance, there are undoubtedly many patients who have had previous chemotherapy, and have drug-resistant organisms as a consequence, who would present themselves as new cases of the disease if a mass campaign were embarked upon. It is therefore of interest that there was evidence from a small number of cases in this study that patients who presented isoniazid-resistant organisms, whether primary or following previous treatment, fared rather less well than patients who had had no previous chemotherapy and had sensitive organisms.

There was a group of patients with initially sensitive strains who repeatedly yielded positive cultures in the later months of treatment, the strains being resistant to isoniazid. These 16 patients, who represented 10% of the survivors at 12 months, should be regarded as a potential public health risk. The catalase activity of the strains from these patients is of particular interest in view of the association between the catalase activity of tubercle bacilli and their virulence to the guinea-pig, and possibly also to man (Middlebrook & Dressler, 1954; Schweiger & Vandra, 1958). The tests showed that the resistant strains from nine of the 16 patients had normal catalase activity, and so may have been virulent.

The possibility that atypical mycobacteria—that is, mycobacteria other than *Myco. tuberculosis*—might be occurring in the patients under study, and might indeed be the cause of their disease, was particularly investigated. A range of identification tests was undertaken on a sample of the patients, and these will be the subject of a separate report. In addition, the colonial appearances of the growth on Löwenstein-Jensen medium, the results of the sensitivity tests and the catalase activity of the strains, all of which were investigated as a matter of routine before and during treatment, provided evidence that the organisms were in fact tubercle bacilli. On the basis of these findings it is believed that atypical organisms were not cultured before the start of treatment from any patient in this study. Cultures containing small numbers of mycobacteria other than tubercle bacilli were obtained occasionally during the course of treatment.

Smear-positive, but culture-negative, results, which were very uncommon before the start of treatment, increased in frequency during the earlier months of therapy, becoming less common again in the second six months. A detailed analysis of the data suggests that these smear-positive culture-negative results, obtained in patients on the combination of isoniazid and PAS, represented non-viable bacilli; they were thus classed as bacteriologically negative results.

Information has accumulated during the course of the study which suggests that Indian strains of tubercle bacilli differ from British strains in their behaviour in PAS-sensitivity tests. It seems likely that it will prove necessary, in the case of Indian strains, to use standards for resistance which are different from those in current use when classifying

British strains. Further work on this subject is in progress and will be reported later.

Finally, the results reported here relate only to a period of one year. A second year of treatment is being investigated in order to study relapse and its prevention, and these results will be reported later. Further, the study of the contacts of both series of patients, which is also in progress, will give information on whether the contacts of patients treated at home are exposed to special risk of infection. The Chemotherapy Centre is also undertaking further investigations into problems of domiciliary chemotherapy; a controlled study of the relative merits of different chemotherapeutic combinations in domiciliary patients is in progress, the contacts also being followed. It is hoped that these various studies will assist further in the planning of mass campaigns against tuberculosis.

XV. SUMMARY

1. In all, 193 patients were admitted to a comparison of treatment at home (96 patients) with treatment in sanatorium (97 patients) for a period of 12 months, the patients being allocated at random to one of these two treatment series.

2. Patients in both series were given the same chemotherapy for the 12 months—namely, isoniazid 200 mg plus PAS (sodium) 10 g daily (given together in the same cachet in two doses) for patients weighing 100 lb. (45 kg) or more. The dosage was reduced for lighter patients, the range of dosage being from 3.7 to 6.6 mg isoniazid/kg body-weight and from 0.19 to 0.33 g PAS (sodium)/kg body-weight.

3. Although all the survivors were examined at 12 months, the main analysis in this report concerns the 82 home and 81 sanatorium patients who (*a*) had organisms sensitive to the two drugs, (*b*) had had little or no previous chemotherapy and (*c*) followed the allocated treatment regimen.

4. The intake of patients began on 24 September 1956 and ended on 24 September 1957.

5. On admission to treatment, and in spite of the random allocation of treatment, the home series had more severe disease than the sanatorium series in respect of extent of cavitation, total extent of the disease, and bacterial content of the sputum, although the series were similar in other respects; the pretreatment differences between the series were greater for the females than for the males.

6. When the 49 *males* at home were compared with the 50 males in sanatorium, it was found that the males in sanatorium had gained more weight and had shown the greater reduction in the ESR. On the other hand, the benefit in terms of radiographic change was only slight, and the two series had fared similarly in respect of cavity closure and reduction in cavity size. The two series had also responded very similarly bacteriologically, and at 12 months 9% of 44 home and 10% of 48 sanatorium patients yielded positive cultures; in terms of the total number of patients for whom cultures were examined, 9% of those at home and 4% of those in sanatorium yielded isoniazid-resistant cultures. Using very stringent criteria to assess the bacteriological status at the end of 12 months, 10% of the home and 10% of the sanatorium patients still had active disease bacteriologically; one patient in each series had died of tuberculosis.

7. The direct comparison of the 33 *females* at home with the 31 in sanatorium was less easy to interpret because of the pretreatment differences. The sanatorium series had gained more weight and had shown the greater response in the ESR. This series had also made better radiographic and bacteriological progress. At 12 months, using very stringent criteria, eight (24%) of 33 home and one (3%) of 31 sanatorium patients had active disease bacteriologically; one sanatorium patient (3%) had died of tuberculosis.

8. Statistical standardization of the results, to make allowance as far as possible for the pretreatment differences, suggests that the radiographic progress was similar for patients with similar pretreatment lesions, whether male or female, but the bacteriological disadvantage to the females at home persisted.

9. A study of prognosis in relation to the pretreatment clinical features suggests that a high ESR, extensive cavitation and widespread disease, and, to a lesser extent, a large bacterial content of the sputum, were relatively unfavourable prognostic signs.

10. The self-administration of the cachets was supervised both by tests on the urine and by counts of the stock of cachets, and this revealed a difficulty in obtaining the long-term co-operation of patients treated at home in taking their medicine. More irregularity in self-administration was found among female than among male patients.

11. Toxic manifestations attributed to PAS occurred in 2.6% of the 193 patients. No toxic effects were produced by isoniazid.

12. Thirteen home and six sanatorium patients were admitted to hospital in the course of the 12 months for the investigation or treatment of non-tuberculous conditions. Thus a small number of hospital beds proved to be necessary for the home series, and would be needed in any large-scale scheme for home treatment.

13. Infection with primary isoniazid-resistant organisms occurred in 3.6% of the patients, primary resistance to PAS in 2.6% and primary resistance to streptomycin in 2.2% of the patients.

14. A detailed analysis of smear-positive but culture-negative bacteriological findings has shown that these may be interpreted as negative bacteriological results.

15. There is evidence that different criteria of interpretation should be used for PAS-sensitivity tests on Indian strains of tubercle bacilli from those that apply to British strains.

16. At the start of treatment the great majority of patients had low incomes, by current Indian standards, and came from families with low total incomes.

17. The diet of the home and sanatorium series was similar before the start of treatment, but there were important differences during treatment, the sanatorium diet being clearly superior. Thus, in terms of animal protein, 84% of the males and 97% of the females at home had less than 30 g a day, compared with no patient of either sex in sanatorium.

18. The sanatorium patients had more rest; at 12 months, 19% of males and 10% of females were allowed up for four hours a day, whereas at home 80% of the males and 91% of the females had returned to part-time or full-time activity, both of which represent a greater degree of activity than four hours up for sanatorium patients.

19. The majority of the home patients were living in overcrowded conditions, the families of 68% of the males and 85% of the females having less than 45 sq. ft (4.2 m^2) of living accommodation per person; 20% of the families of the males and 48% of the females had less than 25 sq ft (2.3 m^2) per person. Two more males (4%) were homeless.

20. The income of the males in both series was greatly reduced during treatment but a proportion of the home patients had regained some earning capacity by the end of 12 months, when 55% of the 47 males at home were earning.

21. A modest amount of financial assistance was given to the families of patients in both series, more being required for the families of male than of female patients, and more being required when the patient was treated at home than when he was treated in sanatorium.

22. Whereas major social problems arose in 20 of the families of the 97 patients in sanatorium, they occurred in only eight in the 96 home families, and were also less serious; thus, *in this study*, sanatorium treatment proved more disruptive to family life.

23. Twelve of the 97 sanatorium patients were discharged during the 12 months (though four were only temporary discharges) whereas only one of the 96 home patients discharged himself from treatment. It proved easier to keep the co-operation of the home patients.

24. It is concluded that the results of domiciliary chemotherapy, as carried out in this study, approach sufficiently closely the results of sanatorium treatment to suggest that it is appropriate to treat the majority of patients at home. In formulating this conclusion, consideration has been given to the manifest advantages of sanatorium treatment—namely, rest, diet, nursing and supervised medicine-taking—on the one hand, and the social disadvantages, as represented by the disruption to family life and the difficulty of persuading patients to remain in sanatorium, on the other. It is recognised that the standards of medical care during this study were very favourable, but it is considered that comparable results should be obtainable from a domiciliary service which is being operated from a tuberculosis clinic, provided that certain minimum requirements are met. Among these are an adequate supply of antituberculosis drugs, enough staff, including a

public health nurse and a social worker, transport (including an ambulance), a small number of hospital beds for special cases, an efficient appointment system, a system of surprise checks on the co-operation of the patients in taking their medicines, reliable smear examinations of sputum for tubercle bacilli, and a welfare fund for especially needy patients.

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It would not have been possible to complete the study reported here without the devoted work of the entire staff—clinical, laboratory, statistical, radiographic, secretarial and administrative. The efforts of the public health nurses, health visitors and social workers made a particularly important contribution to keeping the co-operation of the study patients and their families.

RÉSUMÉ

Le Centre de chimiothérapie de la tuberculose, qui exerce son activité sous les auspices de l'Indian Council of Medical Research, du gouvernement de l'Etat de Madras, de l'OMS et du Medical Research Council of Great Britain, a institué une étude comparative des avantages respectifs du traitement à domicile et hospitalier de la tuberculose.

Les malades ont été répartis au hasard en deux groupes: l'un de 96 personnes soignées à domicile, l'autre de 97 malades hospitalisés en sanatorium. Du 24 septembre 1956 au 24 septembre 1957, les malades des deux séries ont reçu la même médication, soit: une dose quotidienne de 200 mg d'isoniazide et de 10 g de PAS sodique (les deux substances étant incorporées dans le même cachet) pour les malades pesant 45 kg ou plus; une dose plus faible pour les malades pesant moins de 45 kg, soit 3,7-6.6 mg d'isoniazide et 0,19 à 0,33 g de PAS sodique, par kg de poids corporel.

Bien que les malades aient été répartis au hasard dans les deux séries, ceux qui composaient le groupe soigné à domicile étaient plus gravement atteints que les malades en sanatorium, sous le rapport de l'étendue des cavernes, de l'extension de la maladie et de la teneur des crachat en bacilles. Les différences constatées entre les séries avant le traitement étaient plus grandes chez les femmes que chez les hommes.

Tous les survivants ont été examinés à la fin du douzième mois. Ce rapport analyse principalement les observations faites sur 82 malades soignés à domicile et 81 malades soignés en sanatorium, qui tous: *a)* étaient porteurs de bacilles sensibles à l'action des deux médicaments; *b)* n'avaient pas reçu de traitement chimiothérapique antérieur, ou à peu près pas; *c)* avaient suivi le schéma de traitement prescrit.

Les 50 hommes traités en sanatorium avaient gagné plus de poids que les 49 hommes traités à domicile; leur vitesse de sédimentation globulaire s'était abaissé plus nettement. En revanche, ils ne présentaient, à la radiographie, qu'une faible amélioration. Dans les deux séries, la régression des cavernes était à peu près la même. C'était le cas aussi de la réponse bactériologique au traitement: après 12 mois, 9% des malades à domicile et 10% des malades en sanatorium présentaient des cultures positives. Le test bactériologique a révélé chez 9% et 4% des malades respectivement des cultures résistantes à l'isoniazide.

Il a été plus difficile d'interpréter les résultats d'une comparaison directe entre les 33 femmes soignées à domicile et les 31 soignées en sanatorium, ceci en raison des différences existant avant le traitement. Les malades en sanatorium avaient plus que les autres augmenté de poids et amélioré leur vitesse de sédimentation. Elles avaient également fait de plus grands progrès, révélés par l'examen radiologique et bactériologique. Après 12 mois, en appliquant des critères très sévères, on a calculé que 8 des 33 femmes soignées à domicile, soit 24%, et 1 des 33 femmes en sanatorium (3%) présentaient une tuberculose bactériologiquement évolutive. Une malade du sanatorium est morte de tuberculose.

L'analyse statistique des résultats, en vue de tenir compte autant que possible des différences observées avant le traitement a donné les indications suivantes: les progrès révélés par la radiographie étaient semblables pour les malades — hommes et femmes — qui présentaient des lésions analogues avant le traitement; du point de vue bactériologique, la situation restait défavorable pour les femmes soignées à domicile.

Pour vérifier que les malades prenaient régulièrement leurs médicaments, on a procédé à des analyses d'urine et dénombré les provisions de cachets. On a pu se convaincre qu'il est difficile d'obtenir des malades traités à domicile qu'ils prennent leurs remèdes consciencieu-

sement pendant une longue période. A cet égard, les femmes se sont révélées moins régulières que les hommes.

Des manifestations toxiques attribuées au PAS sont apparues chez 2,6 % des 193 malades. L'isoniazide n'a produit aucun effet toxique.

Treize malades à domicile et 6 malades en sanatorium ont été admis à l'hôpital au cours des 12 mois pour des affections non tuberculeuses. Il faut donc prévoir un certain nombre de lits pour les malades traités à domicile, et cette nécessité existerait pour tout grand programme de soins à domicile.

Parmi les malades non inclus dans les groupes étudiés, 3,6% étaient infectés par des bacilles présentant une résistance primaire à l'isoniazide, 2,6% par des bacilles résistants au PAS et 2,2% par des bacilles résistants à la streptomycine. Il semble que les tests de résistance au PAS appliqués aux souches anglaises de bacilles ne conviennent pas à l'estimation de la résistance des souches indiennes, pour lesquelles il faudrait instituer d'autres critères.

Au début du traitement, la grande majorité des malades appartenaient aux classes économiquement faibles de la population. Alors que les malades des deux groupes vivaient à peu près selon le même régime alimentaire avant le début du traitement, ceux du groupe traités en sanatorium furent de ce fait grandement favorisés, la nourriture hospitalière étant nettement supérieure à la nourriture familiale. C'est ainsi que 84% des hommes et 97% des femmes traités à la maison recevaient moins de 30 g par jour de protéines animales. Aucun malade en sanatorium n'était réduit à cette extrémité. Les malades hospitalisés jouissaient aussi de plus de repos. Au douzième mois, 19% des hommes et 10% des femmes hospitalisés se levaient pendant 4 heures chaque jour, tandis que, à la même époque, 80% des hommes et 91% des femmes traités à la maison avaient repris une activité totale ou partielle dépassant de beaucoup 4 heures quotidiennes.

La plupart des malades à domicile vivaient dans des conditions de surpeuplement, les familles de 68% des hommes et de 85% des femmes disposant de moins de 4 m^2 par personne, tandis que pour 20% des familles des hommes et 48% de celles des femmes, cette surface dépassait à peine 2 m^2. Deux hommes étaient sans foyer.

Dans les deux groupes, la maladie a fortement diminué le revenu des patients. Pourtant au douzième mois, 55% des malades à domicile avaient retrouvé une certaine capacité de travail et gagnaient leur vie. Des allocations modestes ont été attribuées aux malades des deux groupes, celles des hommes supérieures à celles des femmes, et plus importantes pour les malades à domicile que pour les hospitalisés.

Les problèmes sociaux créés par la maladie et le traitement ont été beaucoup plus sensibles chez les malades en sanatorium et se sont manifestés chez 20 des 97 familles, contre 8 des 96 familles de malades à domicile. On a observé, lors de cette étude, que la vie en sanatorium perturbait davantage la vie familiale. Douze des 97 malades hospitalisés ont quitté le sanatorium au cours des douze mois (4 temporairement), tandis qu'un seul des malades soignés à la maison se soustrayait délibérément au traitement. L'esprit de collaboration était meilleur dans le groupe des malades à domicile.

En conclusion, il semble que les résultats du traitement à domicile sont assez proches de ceux que l'on obtient en sanatorium pour le considérer comme la solution la plus favorable dans la plupart des cas. On ne méconnaît pas pour autant les avantages du traitement en sanatorium: repos, meilleur régime alimentaire, soins infirmiers, contrôle de l'administration des médicaments; mais on tient compte aussi de ses inconvénients sociaux: perturbation de la vie familiale, difficulté d'obtenir des malades qu'ils restent en sanatorium pendant la période de traitement. Sans doute la qualité des soins médicaux assurés aux groupes participant à cette étude était-elle particulièrement favorable. Mais on estime que des résultats analogues pourraient être obtenus grâce à un service de soins à domicile qui dépendrait d'un dispensaire antituberculeux, à condition toutefois que certaines conditions minimums soient respectées, les suivantes par exemple: approvisionnement suffisant en médicaments antituberculeux, personnel assez nombreux (comprenant une infirmière de la santé publique et un travailleur social), moyens de transport (dont une ambulance), un petit nombre de lits d'hôpital pour des cas spéciaux, un système efficace de visites, un dispositif pour vérifier à l'improviste au domicile du malade s'il prend régulièrement ses médicaments, la possibilité d'examens d'étalements de crachats pour la recherche du bacille tuberculeux, et un fonds d'assistance pour les malades particulièrement nécessiteux.

REFERENCES

Andrews, R. H. & Radhakrishna, S. (1959) *Tubercle (Lond.)*, **40**, 155

Benjamin, P. V. (1946) *Memorandum submitted to the Health Survey and Development Committee ; Volume I, Report of the Health Survey and Development Committee*, Calcutta, Government of India Press, p. 97

Bönicke, R. (1958) *Bull. int. Un. Tuberc.*, **28**, 153

Bowerman, E. (1957) In: *Transactions of the 16th Conference on the Chemotherapy of Tuberculosis held February 11th to 14th, 1957, at St Louis, Missouri, by the Veterans Administration*, Washington, p. 71

Chaudhuri, S (1959) *Lancet*, **1**, 144

Coster, J. F. & Manten, A. (1956) *Amer. Rev. Tuberc.*, **74**, 958

Courdurier, J. & Brygoo, E. (1947) *Méd. trop.*, **7**, 254

Crofton, J. (1957) *Newc. med. J.*, **25**, 45

Daniels, M., Ridehalgh, F., Springett, V. H. & Hall, I. M. (1948) *Tuberculosis in young adults*, London, Lewis, p. 217

Dixon, W. M., Stradling, P. & Wootton, I. D. P. (1957) *Lancet*, **2**, 871

East African/British Medical Research Council Sulphone Investigation (1959) *Tubercle (Lond.)*, **40**, 1

Fox, W. (1958) *Tubercle (Lond.)*, **39**, 269

Fox, W., Hutton, P. W., Sutherland, I. & Williams, A. W. (1956) *Tubercle (Lond.)*, **37**, 435

Fox, W. & Sutherland, I. (1956) *Quart. J. Med.*, **25**, 221

Fox, W., Sutherland, I. & Daniels, M. (1954) *Quart. J. Med.*, **23**, 347

Fox, W., Wiener, A., Mitchison, D. A., Selkon, J. B. & Sutherland, I. (1957) *Tubercle (Lond.)*, **38**, 71

Frimodt-Møller, J. (1949) In: *Proceedings of the Seventh Tuberculosis Workers' Conference held in Bombay, November 1949, under the auspices of the Tuberculosis Association of India*, New Delhi, p. 271

Frimodt-Møller, J. (1955) *Indian J. Tuberc.*, **2**, 47

Frimodt-Møller, J., Jesudian, K. T., Muthiah, T. S. & Barton, R. M. (1953) *Indian J. Tuberc.*, **1**, 23

Frimodt-Møller, J., Jesudian, K. T., Muthiah, T. S. & Barton, R. M. (1954) *Indian J. Tuberc.*, **1**, 45

Great Britain, Medical Research Council, Tuberculosis Chemotherapy Trials Committee (1953a) *Lancet*, **2**, 213

Great Britain, Medical Research Council, Tuberculosis Chemotherapy Trials Committee (1953b) *Brit. med. J.*, **2**, 1005

Great Britain, Medical Research Council, Tuberculosis Chemotherapy Trials Committee (1955) *Brit. med. J.*, **1**, 435

Holst, E., Mitchison, D. A. & Radhakrishna, S. (1959) *Ind. J. med. Res.*, **47**, 495

Howells, C. H. L. & Swithinbank, J. (1957) *Tubercle (Lond.)*, **38**, 1

Hutton, P. W., Lutalo, Y. K., Williams, A. W., Tonkin, I. M. & Fox, W. (1956) *Tubercle (Lond.)*, **37**, 151

India, Ministry of Commerce, Office of the Economic Adviser (1949) *Report on an enquiry into the family budgets of middle class employees of the Central Government*, Simla, p. 2

India, Ministry of Health, Environmental Hygiene Committee (1950) *Report of the ... October 1949*, Simla, p. 21

Indian Council of Medical Research (1959) *Special Report Series*, No. 34, New Delhi, p. 75

Kreis, B. & Le Joubioux, E. (1957) *Rev. franç. Ét. clin. biol.*, **2**, 447

Kreis, B., Le Joubioux, E. & Pariente, D. (1956) *Ann. Inst. Pasteur*, **91**, 932

McGregor, I. A. & Deegan, T. (1954) *Ann. trop. Med. Parasit.*, **48**, 220

Middlebrook, G. & Dressler, S. H. (1954) *Amer. Rev. Tuberc.*, **70**, 1102

Mitchison, D. A. & Monk, M. (1955) *J. clin. Path.*, **8**, 229

Schweiger, O. & Vandra, E. (1958) *Amer. Rev. Tuberc.*, **78**, 735

Selkon, J. B. & Mitchison, D. A. (1959) *Tubercle (Lond.)*

Simpson, J. McD. (1956) *Tubercle (Lond.)*, **37**, 333

Stewart, S. M. (1955) *J. clin. Path.*, **8**, 237

Tarshis, M. S., Weed, W. A., Parker, M. V. & Dunham, W. B. (1955) *Amer. Rev. Tuberc.*, **72**, 119

Tuberculosis Society of Scotland, Research Committee (1957) *Tubercle (Lond.)*, **38**, 375

Tucker, W. B. & Livings, D. G. (1955) *Amer. Rev. Tuberc.*, **72**, 756

Tyrrell, W. F. (1956) *Lancet*, **2**, 821

Wier, J. A., Curry, F. C., Morse, W. C., Taylor, R. R., Weiser, O. L. & Richey, C. B. (1956) In: *Transactions of the 15th Conference on the Chemotherapy of Tuberculosis held February 6th to 9th, 1956, at St Louis, Missouri, by the Veterans Administration*, Washington, p. 60.

Wier, J. A., Weiser, O. L., Taylor, R. L. & Fraser, R. S. (1957) In: *Transactions of the 16th Conference on the Chemotherapy of Tuberculosis held February 11th to 14th, 1957, at St Louis, Missouri, by the Veterans Administration*, Washington, p. 38

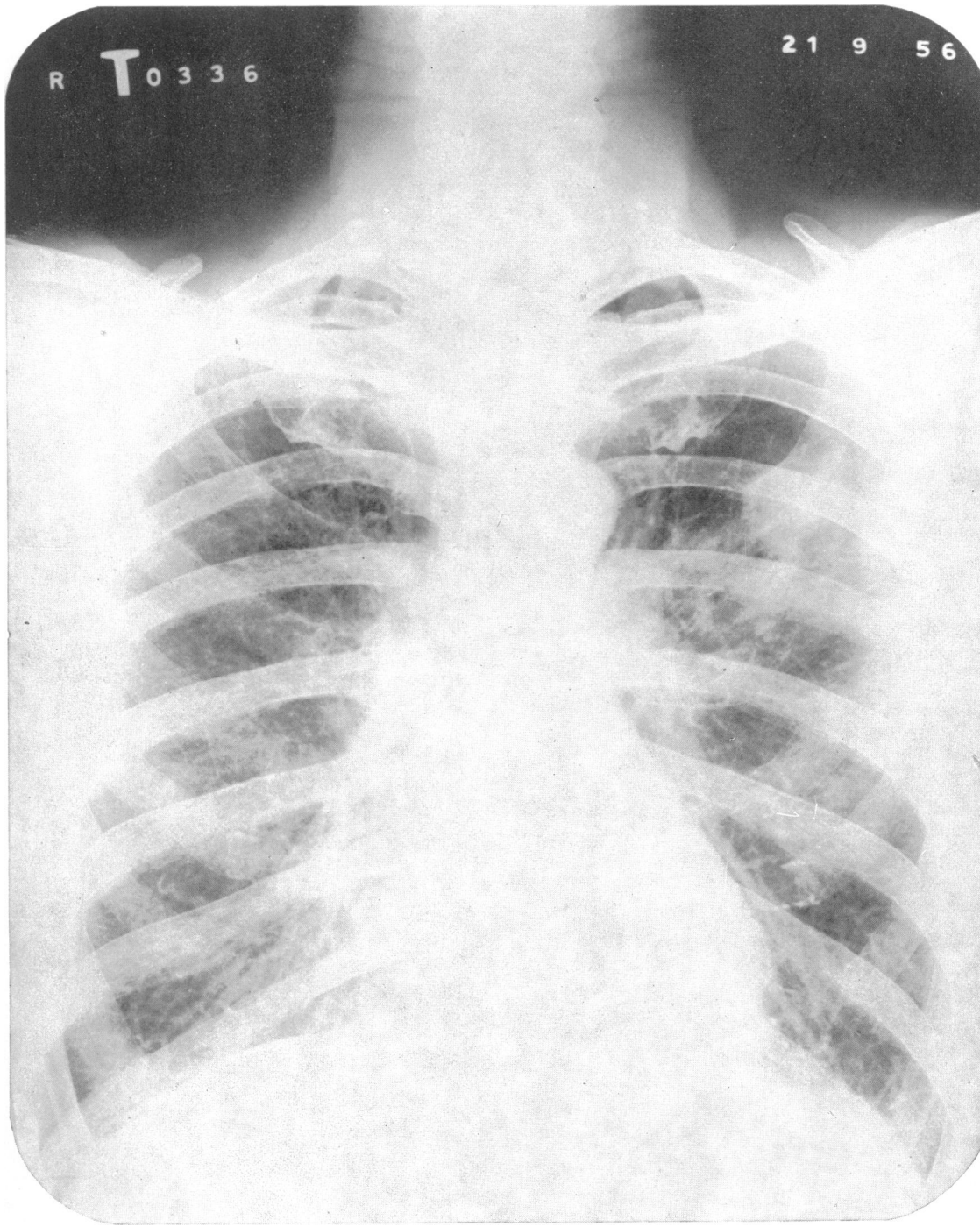
Wolinksy, E., Smith, M. M., Mitchell, R. S. & Steenken, W. (1957) *Amer. Rev. Tuberc.*, **76**, 497

Wynn-Williams, N. & Arris, M. (1958) *Tubercle (Lond.)*, **39**, 138

APPENDIX

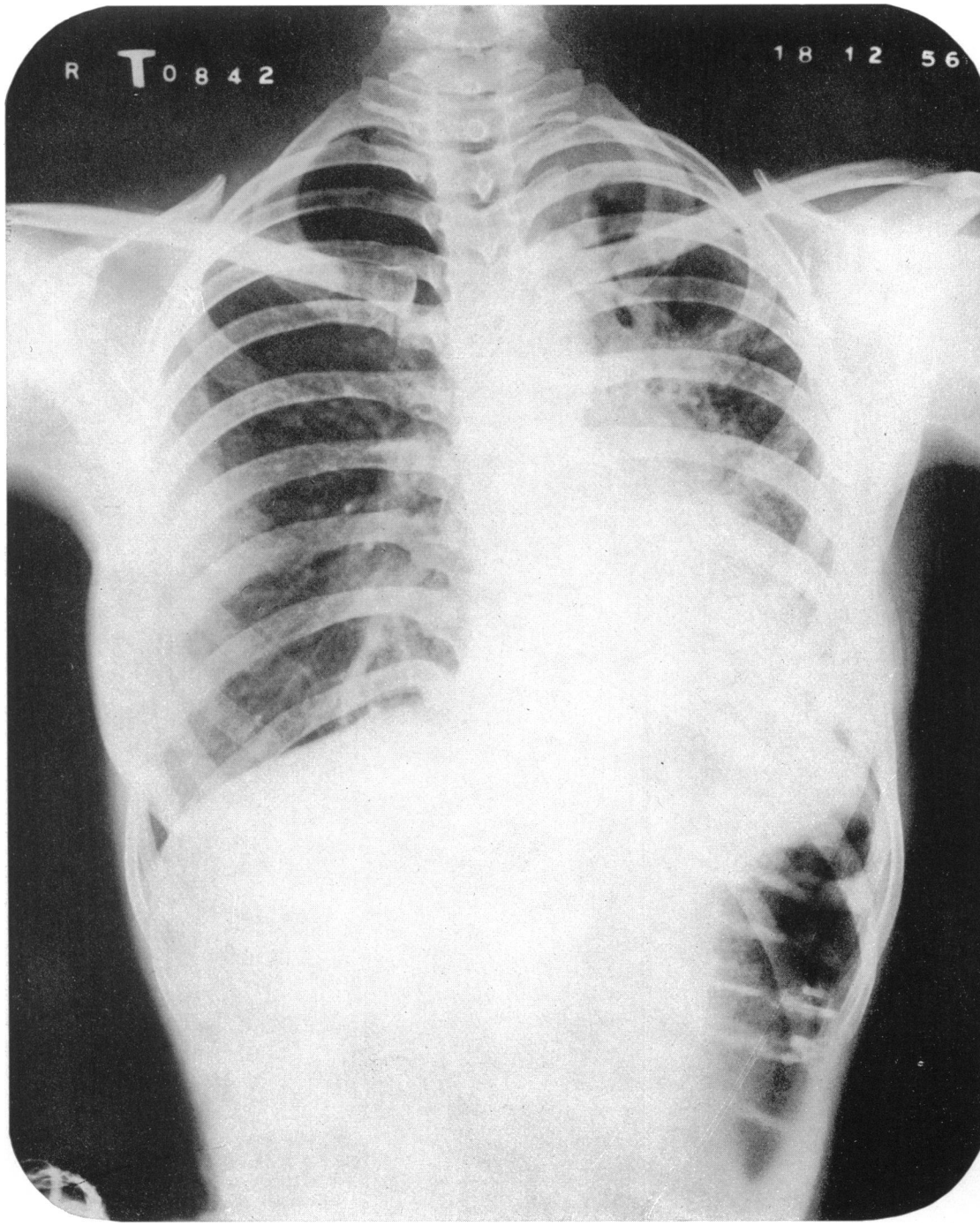
In order to give a clearer picture of the types of pulmonary lesions which the patients in the home series—the series of especial interest—had on admission to treatment, a sample consisting of 10 radiographs, drawn *at random* from among the radiographs of the 82 patients in the home series in the main analysis, is reproduced in this appendix.

MALE AGED 54



Serial No. P 1

FEMALE AGED 20



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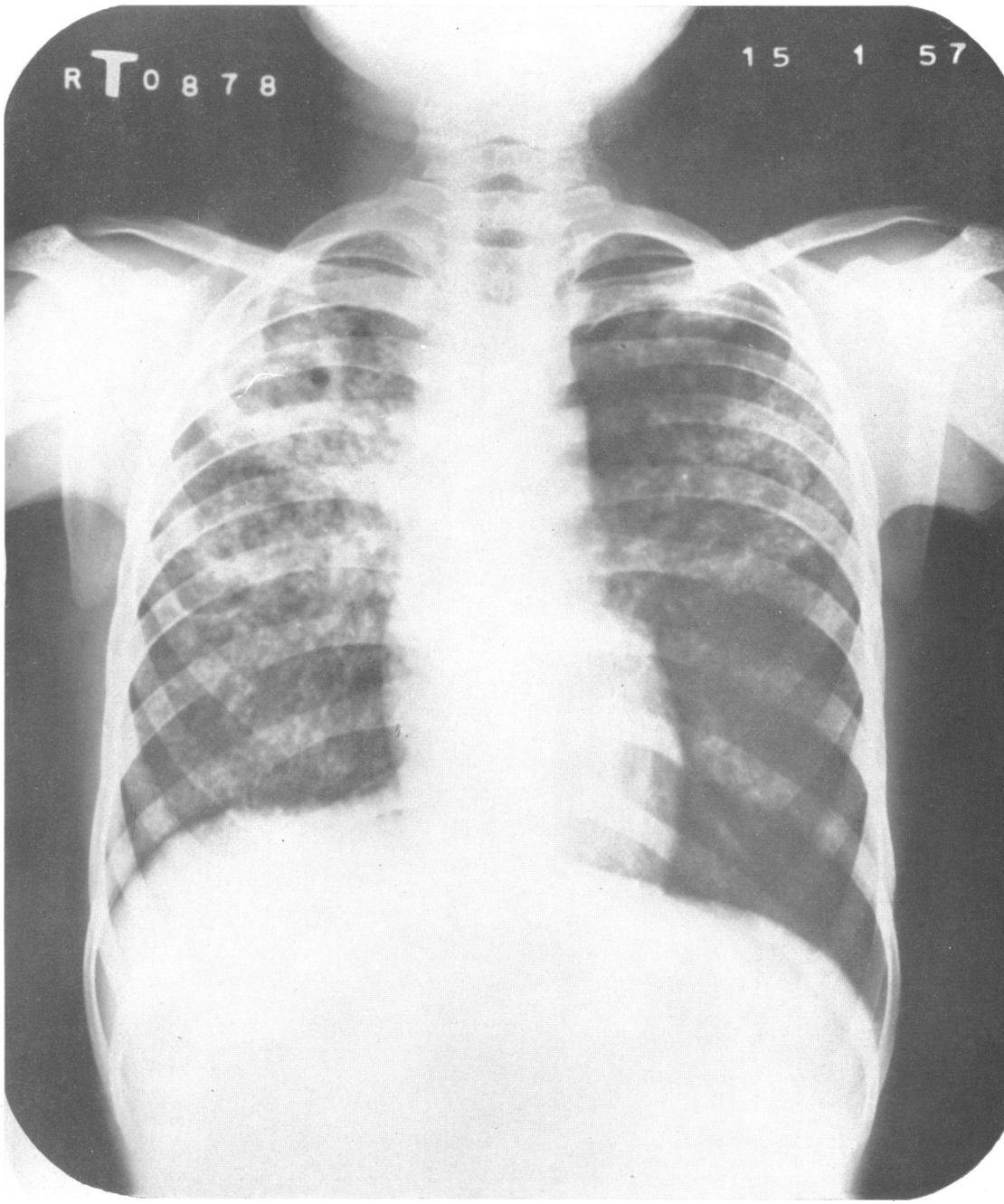
MALE AGED 12



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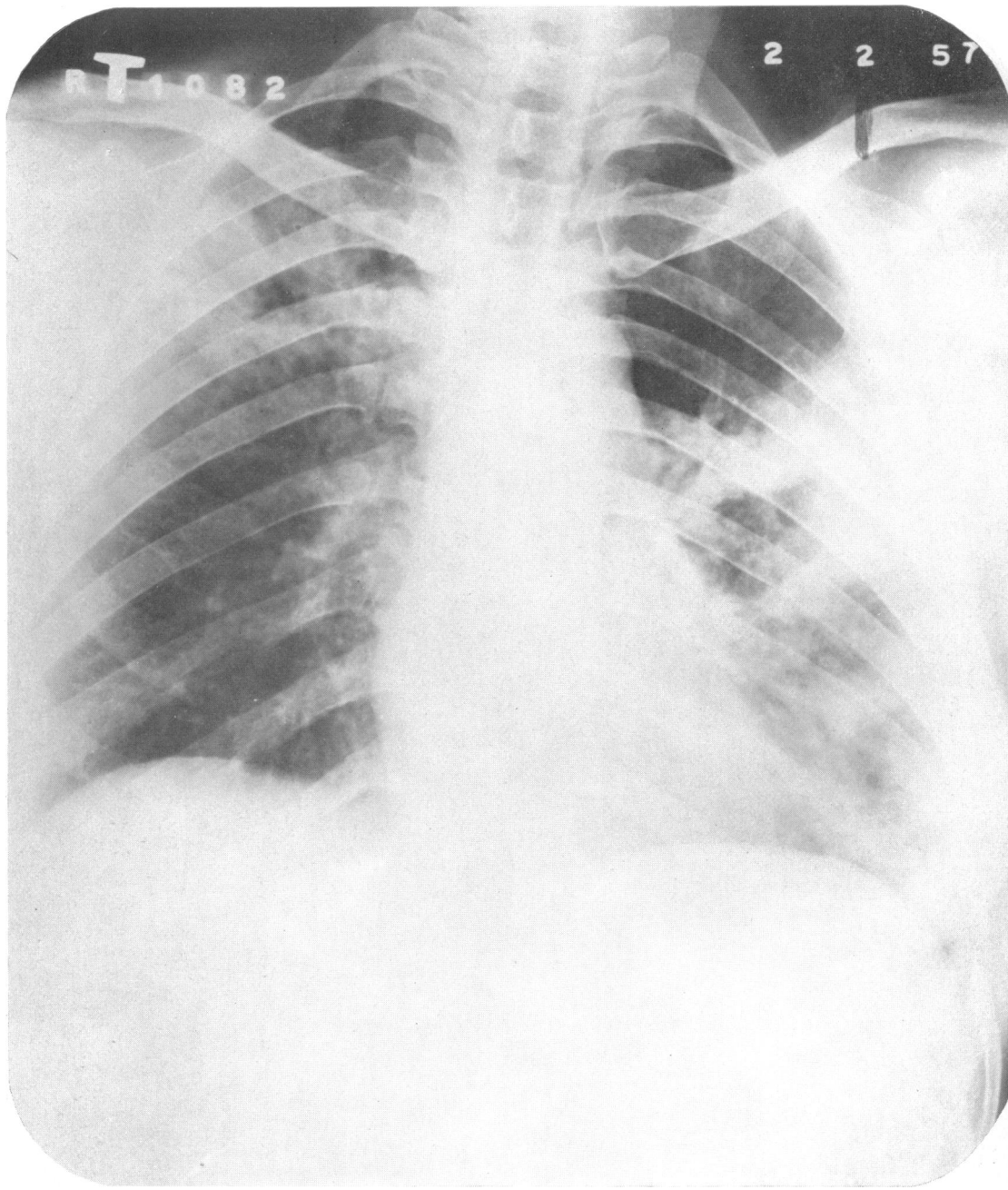

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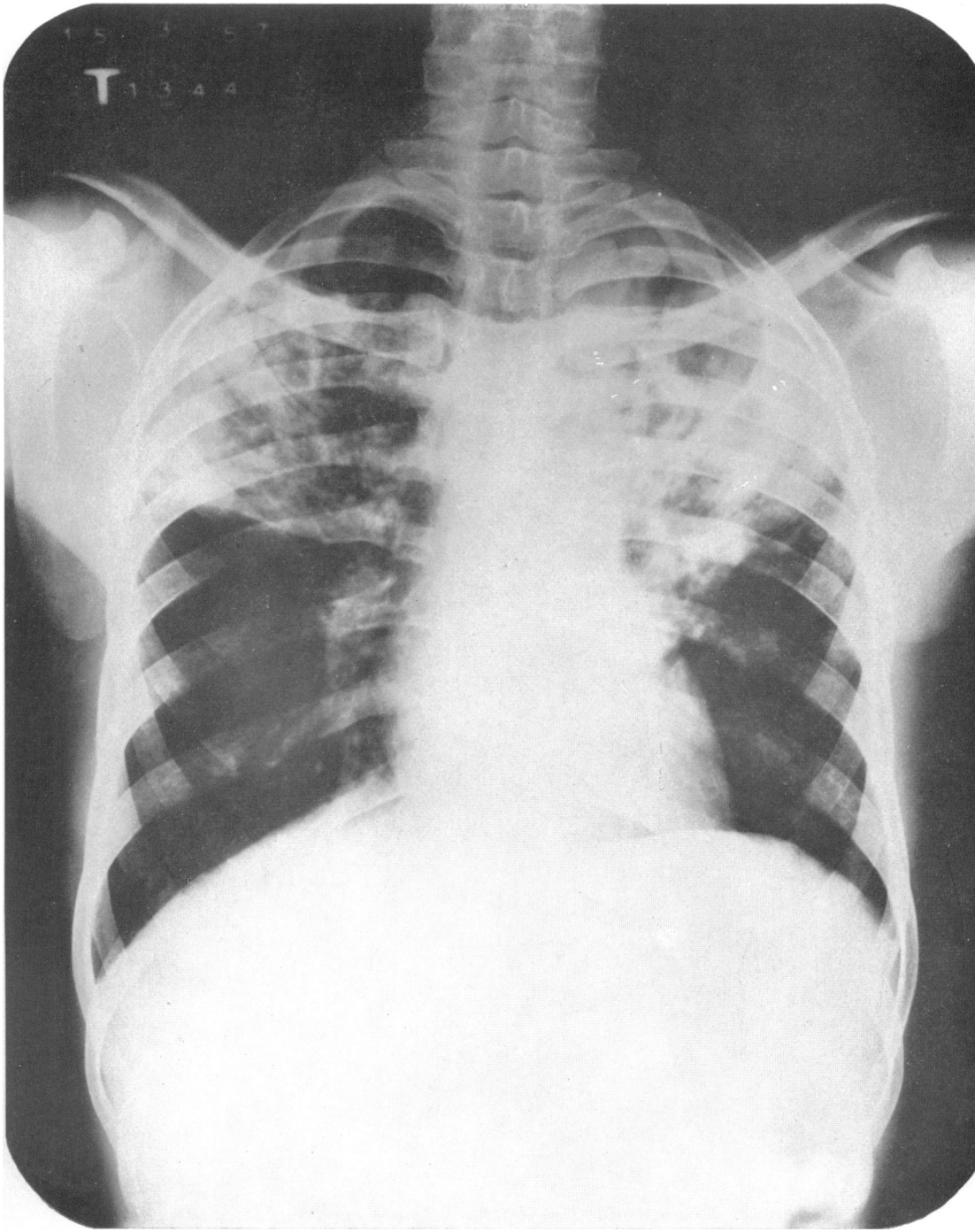
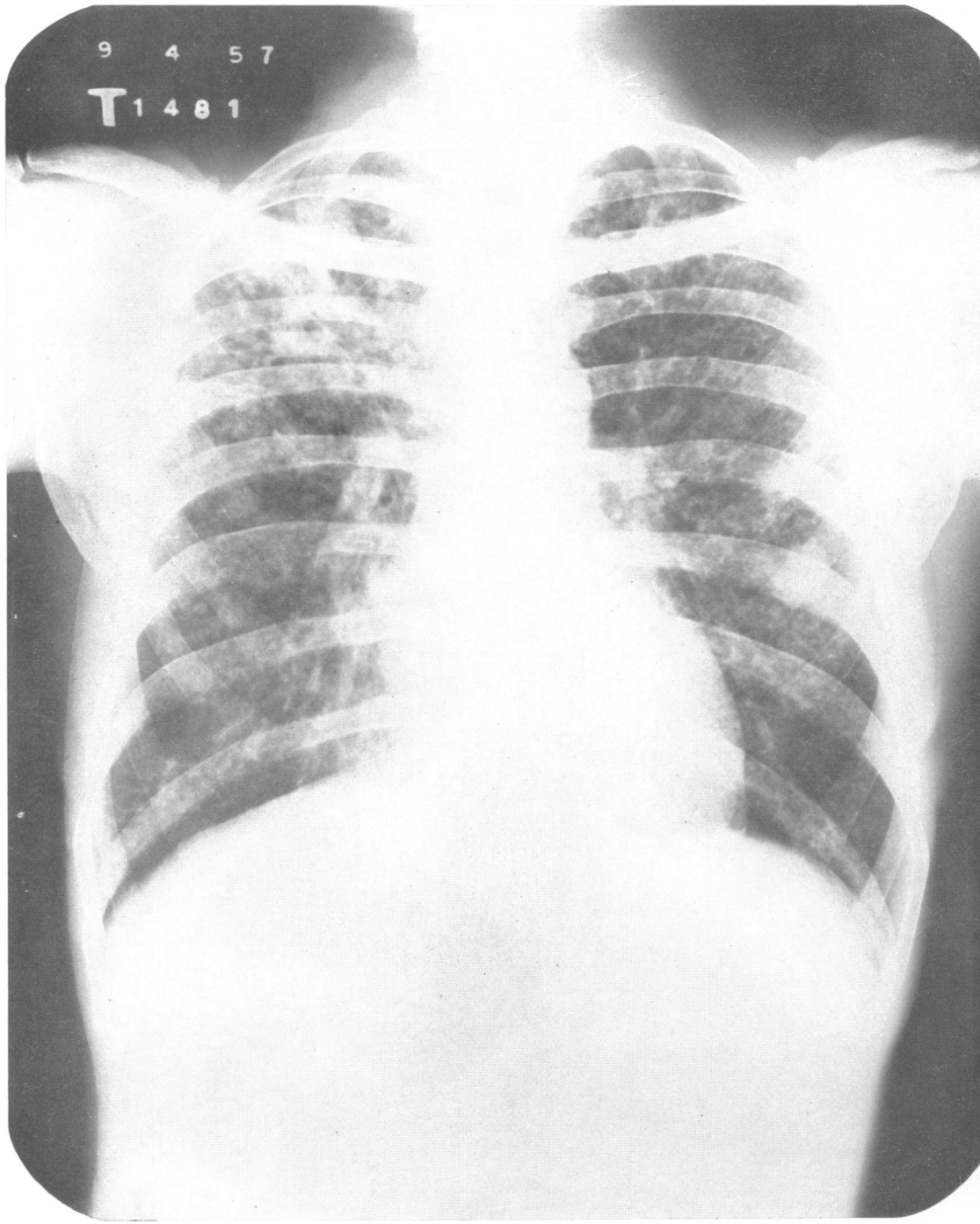


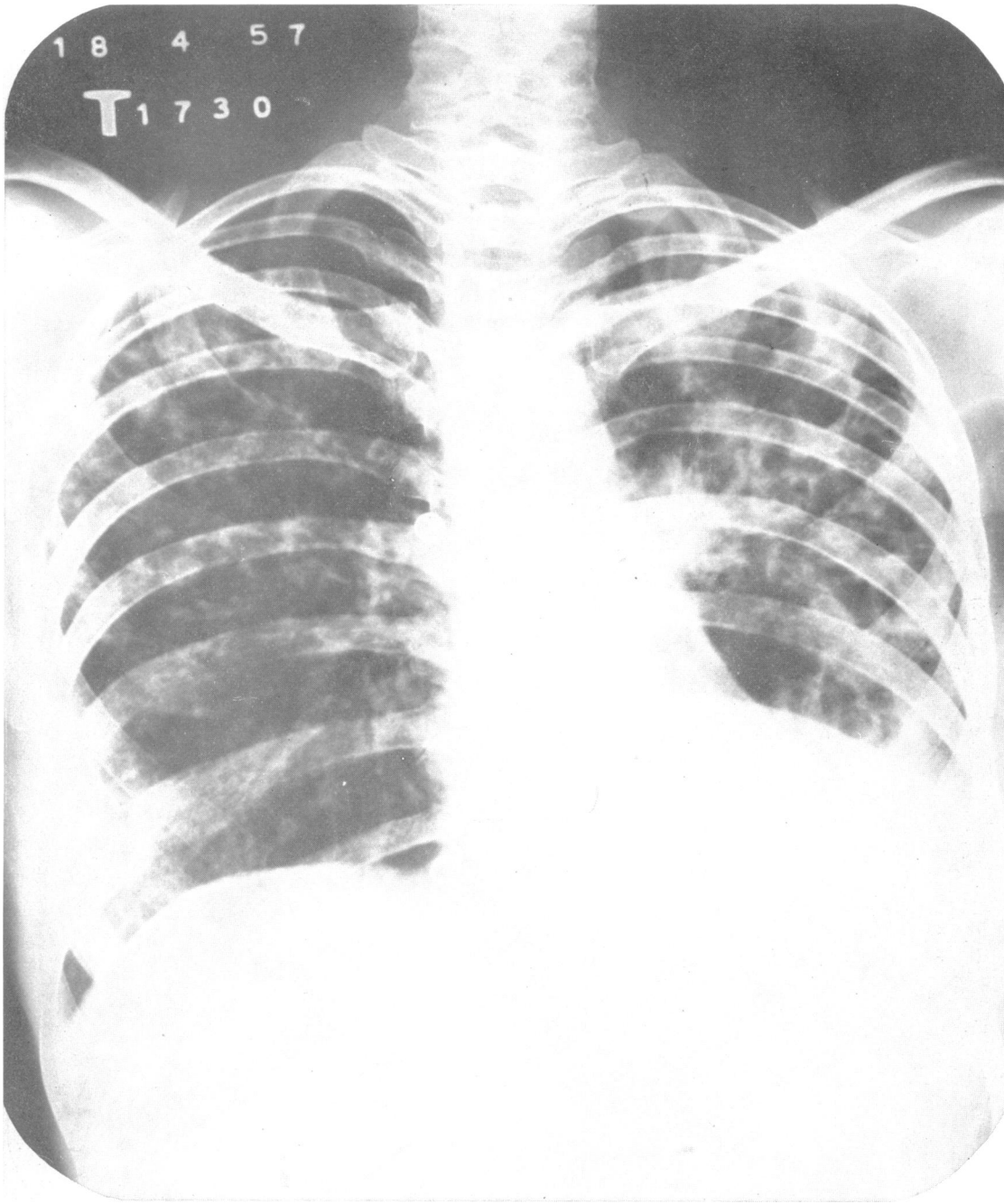
Serial No. P 84

MALE AGED 36



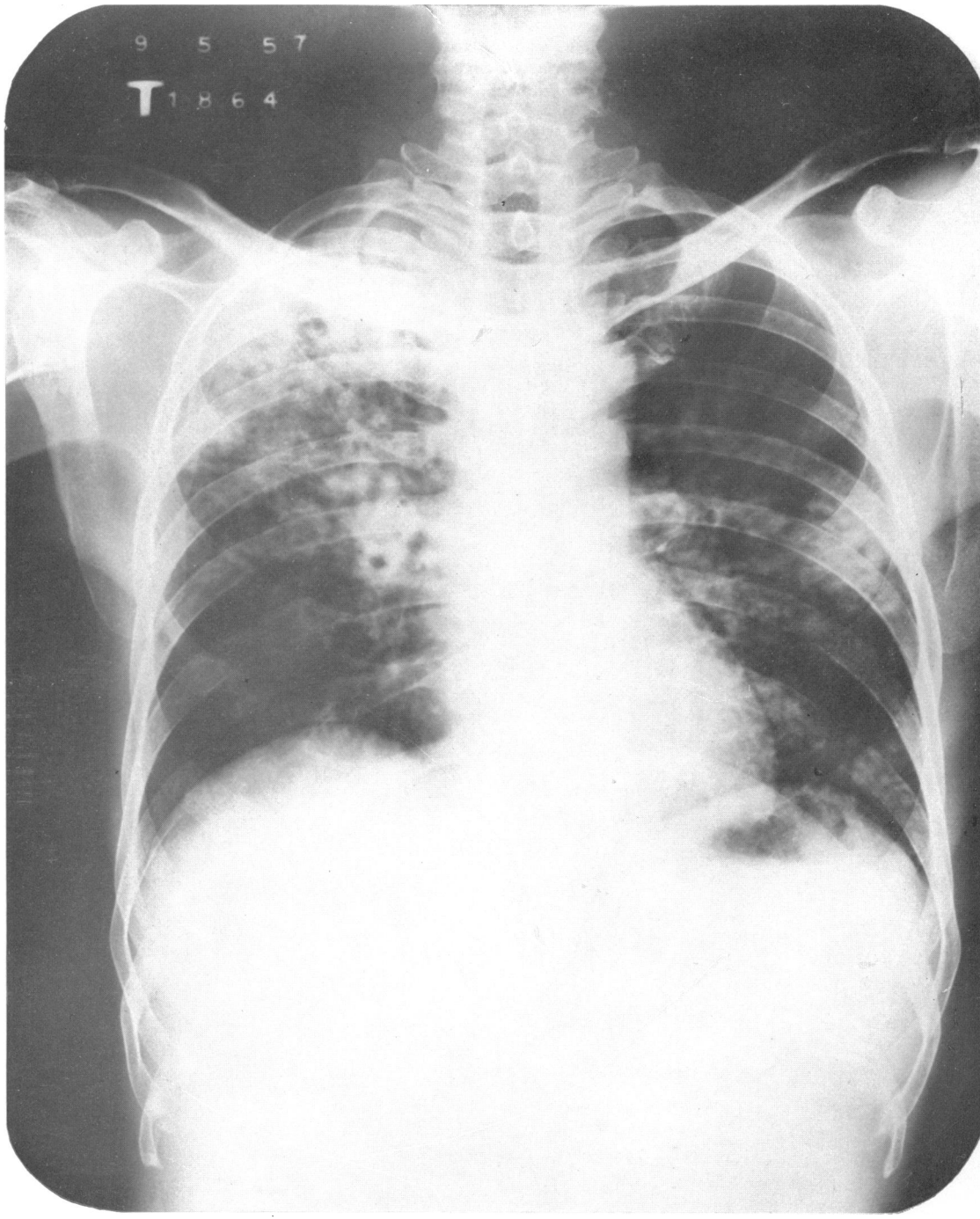
Serial No. P 101

FEMALE AGED 25



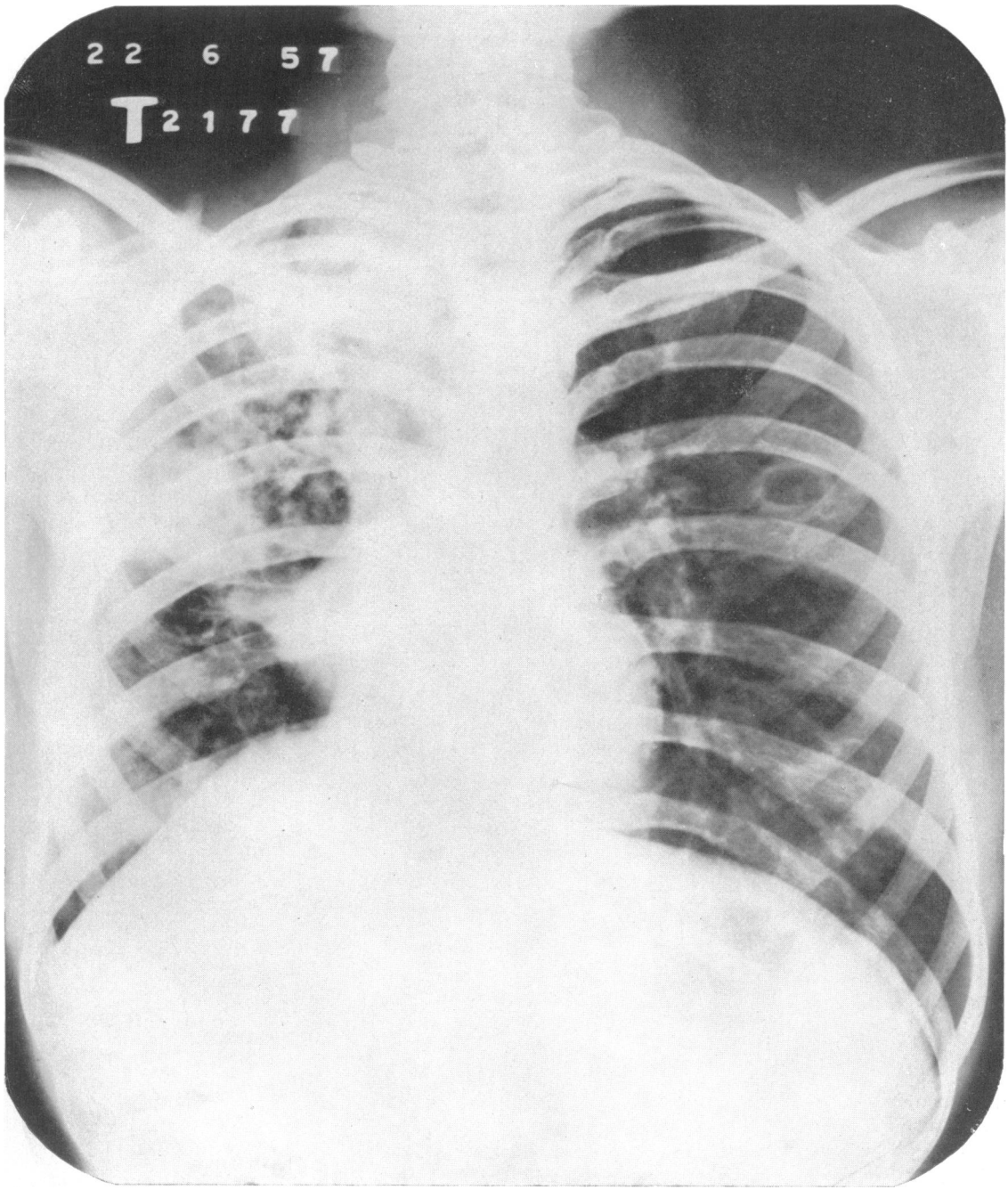
Serial No. P 115

MALE AGED 48



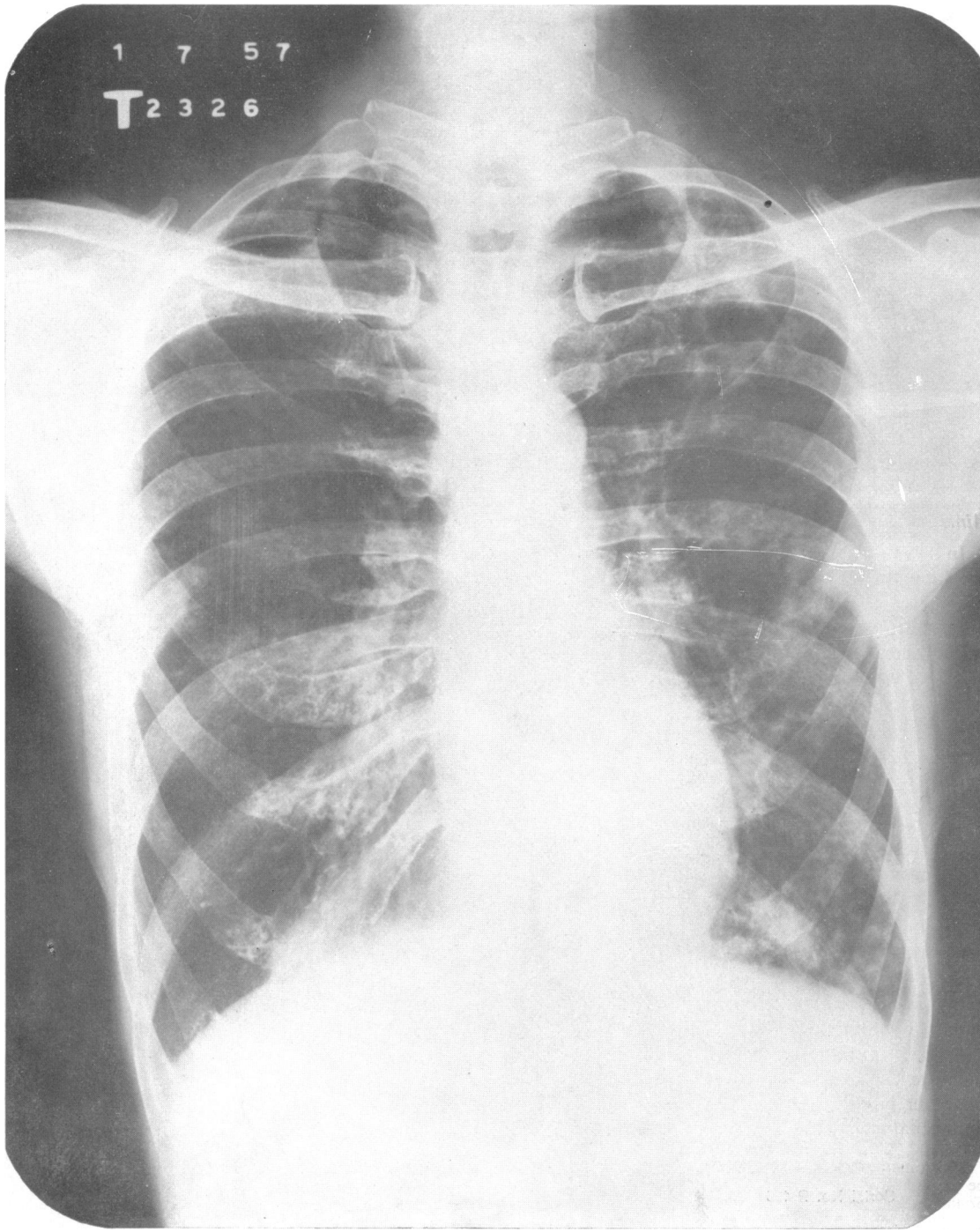
Serial No. P 125

FEMALE AGED 21



Serial No. P 155

MALE AGED 50



Serial No. P 166